

## DESCRIPTION

## AMINOALCOHOL DERIVATIVES

## 5 FIELD OF THE INVENTION

This invention relates to new aminoalcohol derivatives and salts thereof which are beta-3 ( $\beta_3$ ) adrenergic receptor agonists and useful as a medicament.

## 10 BACKGROUND OF THE INVENTION

International Publications No. WO 90/06299, published June 14, 1990, describes derivatives of phenylethanalamines as having an effect on the metabolism, preferably reduction of the blood sugar level and body fat, and International  
15 Publication No. WO 02/32897, published April 25, 2002, describes derivatives of alpha-aryl ethanolamines useful as  $\beta_3$  adrenergic receptor agonists.

## DISCLOSURE OF THE INVENTION

20 This invention relates to new aminoalcohol derivatives which are  $\beta_3$  adrenergic receptor agonists and salts thereof.

More particularly, it relates to new aminoalcohol derivatives and salts thereof which have gut sympathomimetic, anti-ulcerous, anti-pancreatitis, lipolytic, anti-urinary  
25 incontinence, anti-pollakiuria activities, anti-diabetes and anti-obesity, to processes for the preparation thereof, to a pharmaceutical composition comprising the same and to a method of using the same therapeutically in the treatment and/or prevention of gastro-intestinal disorders caused by  
30 smooth muscle contractions in a human being or an animal.

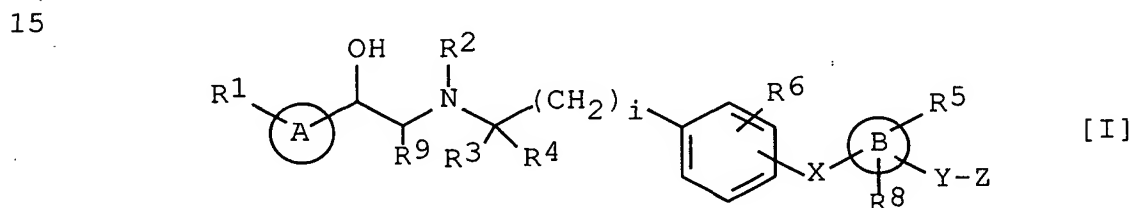
One object of this invention is to provide new and useful aminoalcohol derivatives and salts thereof which have gut sympathomimetic, anti-ulcerous, lipolytic, anti-urinary incontinence, anti-pollakiuria activities, anti-diabetes and  
35 anti-obesity.

Another object of this invention is to provide processes for the preparation of said aminoalcohol derivatives and salts thereof.

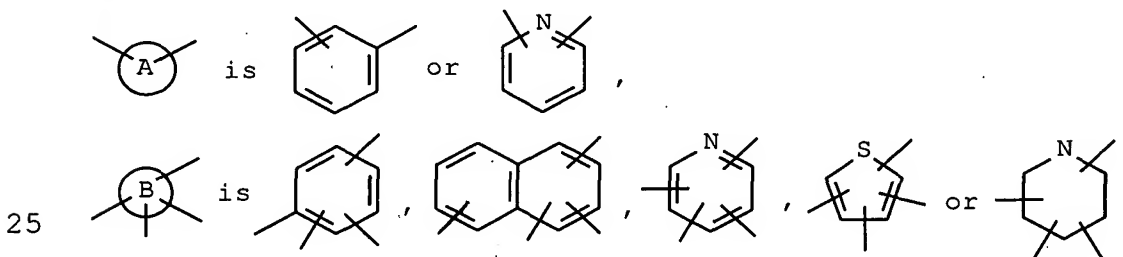
A further object of this invention is to provide a pharmaceutical composition comprising, as an active ingredient, said aminoalcohol derivatives and salts thereof.

Still further object of this invention is to provide a therapeutical method for the treatment and/or prevention of aforesaid diseases in a human being or an animal, using said aminoalcohol derivatives and salts thereof.

The object aminoalcohol derivatives of this invention are new and can be represented by compound of the following formula [I]:



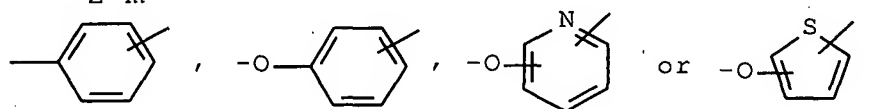
20 wherein



X is bond,  $-\text{CH}_2-$ ,  $-\text{CH}-$ ,  $-\text{C}-$ ,  $-\text{O}-$ ,  $-\text{OCH}_2-$ ,  $-\text{CH}_2\text{O}-$ ,  $-\text{S}-$

or  $-\text{N}-$  (in which  $\text{R}^7$  is hydrogen or lower alkyl),

30 Y is bond,  $-\text{O}-(\text{CH}_2)_n-$  (in which n is 1, 2, 3 or 4),  $-(\text{CH}_2)_m-$  (in which m is 1, 2, 3 or 4),



35 Z is cyano, tetrazolyl, (benzylsulfonyl)carbamoyl,

benzoylsulfamoyl, formyl, carboxy or protected carboxy,

R<sup>1</sup> is hydrogen, lower alkyl or halogen,

R<sup>2</sup> is hydrogen or an amino protective group,

R<sup>3</sup> is hydrogen or lower alkyl,

5 R<sup>4</sup> is hydrogen or lower alkyl,

R<sup>5</sup> and R<sup>8</sup> are each independently hydrogen, halogen, hydroxy,  
lower alkyl, lower alkenyl, lower alkoxy,

hydroxy(lower)alkoxy, mono(or di or

tri)halo(lower)alkoxy, lower alkoxy(lower)alkoxy, lower

10 alkenyloxy, cyclo(lower)alkyloxy,

cyclo(lower)alkyl(lower)alkoxy, benzyloxy, phenoxy,

lower alkylthio, cyclo(lower)alkylthio, lower

alkylsulfonyl, cyclo(lower)alkylsulfonyl, amino,

mono(or di)(lower)alkylamino, mono(or di or

15 tri)halo(lower)alkyl, cyano, piperidinyl or phenyl,

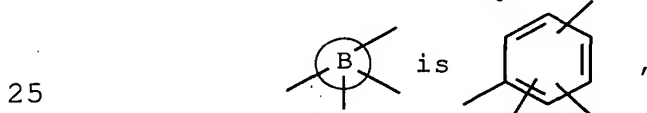
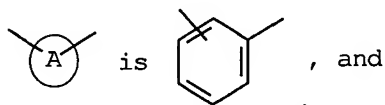
R<sup>6</sup> is hydrogen, lower alkyl or halogen,

R<sup>9</sup> is hydrogen or lower alkyl, and

i is 1 or 2,

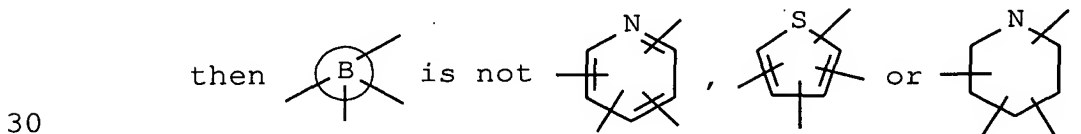
provided that

20 (1) when X is bond,  $-\text{CH}_2-$ ,  $\begin{array}{c} -\text{CH}- \\ | \\ \text{OH} \end{array}$  or  $\begin{array}{c} -\text{C}- \\ || \\ \text{O} \end{array}$ ,



then R<sup>5</sup> is not hydrogen, or

(2) when i is 1,

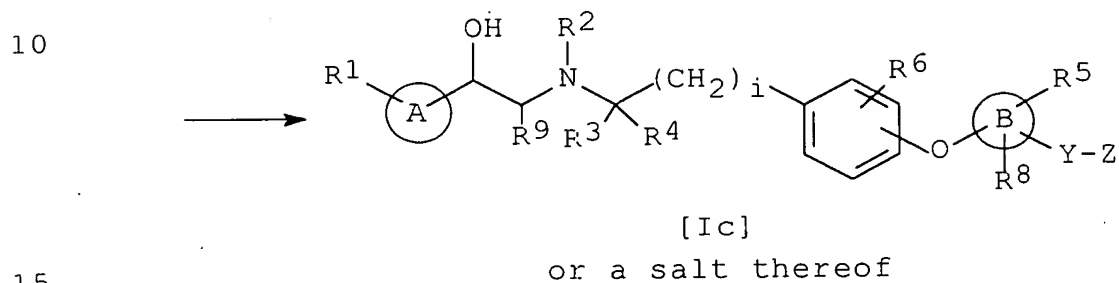
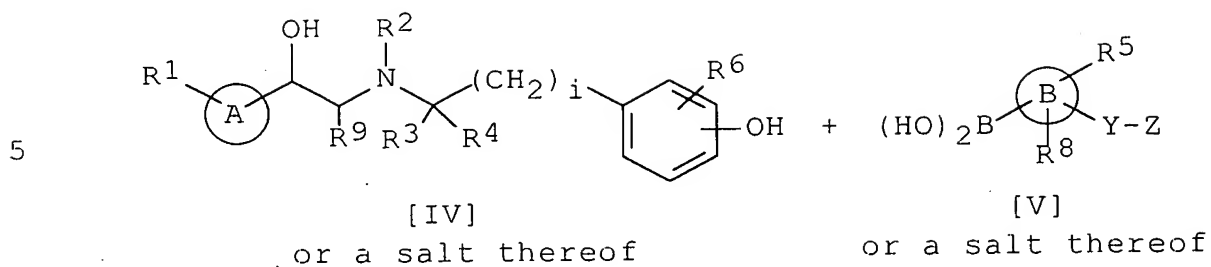
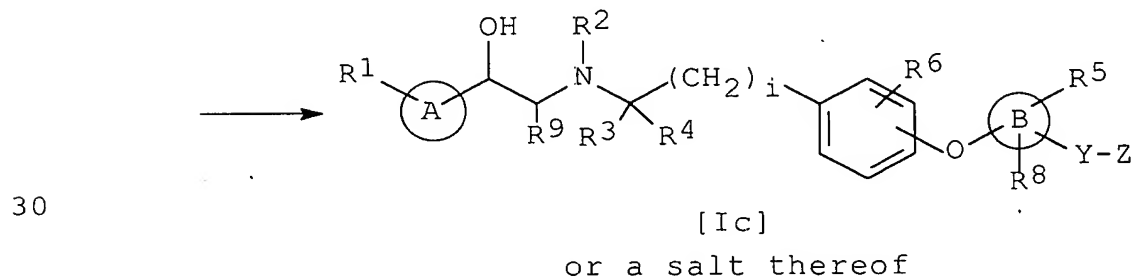
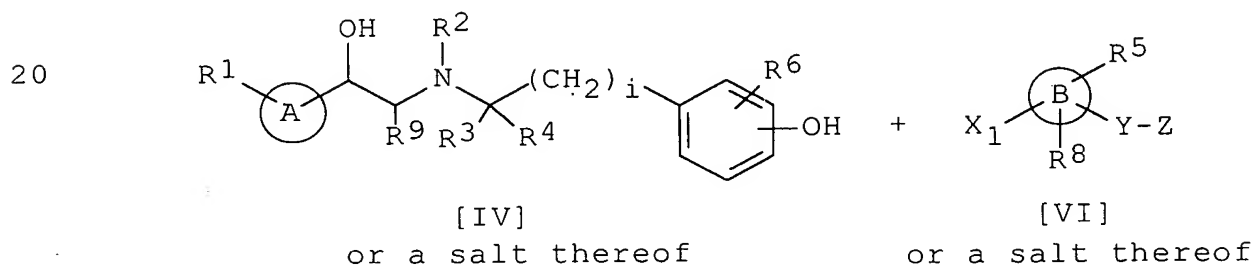


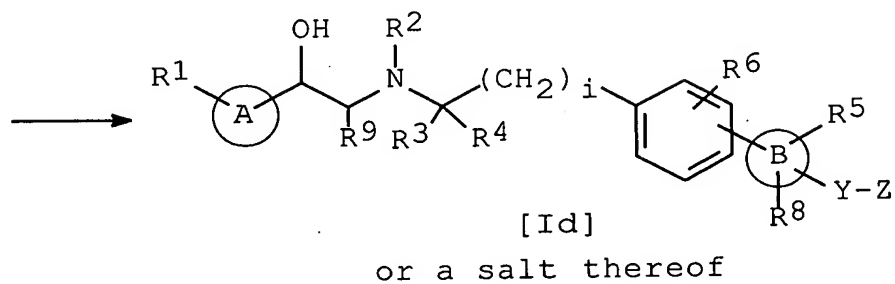
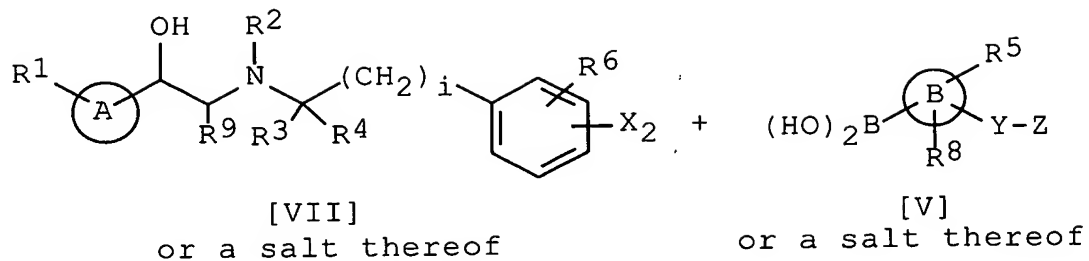
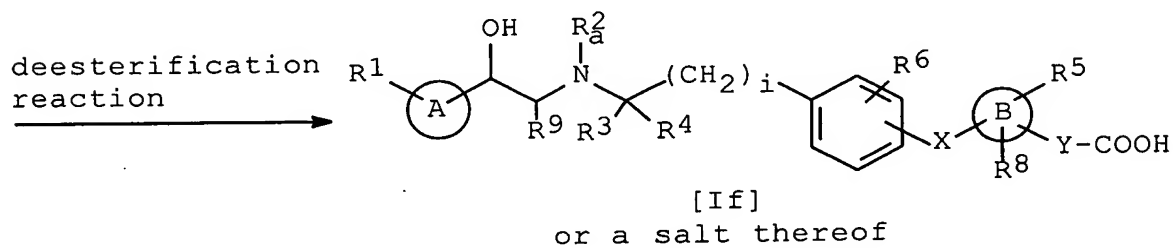
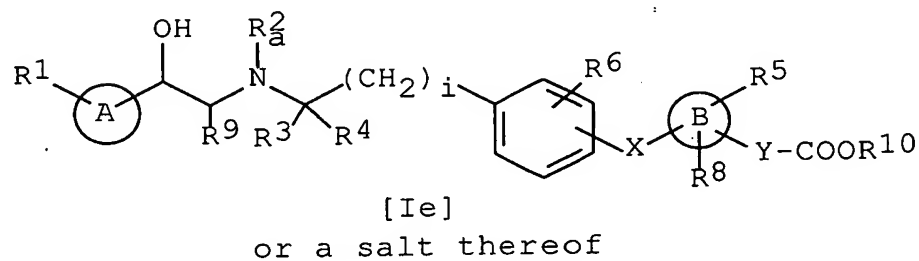
or a salt thereof.

35 According to this invention, the object compounds can  
be prepared by processes which are illustrated in the  
following schemes.



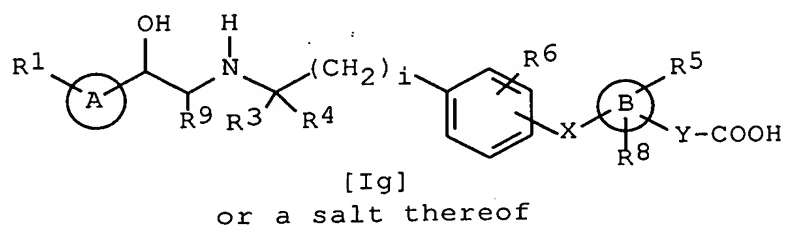


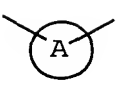
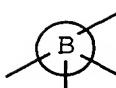
Process 3Process 4

Process 5Process 6

30

elimination reaction  
of the amino  
protective group



wherein  ,  , X, Y, Z, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>,

R<sup>8</sup>, R<sup>9</sup> and i are each as defined above,

R<sub>a</sub><sup>2</sup> is an amino protective group,

5 R<sup>10</sup> is lower alkyl, and

X<sub>1</sub> and X<sub>2</sub> are each a leaving group.

As to the starting compounds [II], [III], [Ia], [IV],  
[V], [VI] and [VII], some of them are novel and can be  
10 prepared by the procedures described in the Preparations and  
Examples mentioned below or a conventional manner.

In the above and subsequent description of the present  
specification, suitable examples of the various definition  
15 to be included within the scope of the invention are  
explained in detail in the following.

The term "lower" is intended to mean a group having 1  
to 6, preferably 1 to 4, carbon atom(s), unless otherwise  
20 indicated.

Suitable "lower alkyl" and "lower alkyl" moiety in the  
terms of "mono(or di)(lower)alkylamino" and "mono(or di or  
tri)halo(lower)alkyl" may include straight or branched one  
25 having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl,  
isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl,  
1-methylpentyl, tert-pentyl, neo-pentyl, hexyl, isohexyl and  
the like.

30 Suitable "lower alkoxy" may include methoxy, ethoxy,  
propoxy, isopropoxy, butoxy, iso-butoxy, tert-butoxy,  
pentyloxy, tert-pentyloxy, hexyloxy and the like, in which  
preferable one is methoxy or ethoxy.

35 Suitable "cyclo(lower)alkyl" moiety in the term of

"cyclo(lower)alkyloxy" may include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, in which preferable one is cyclohexyl.

5           Suitable "halogen" may be fluoro, chloro, bromo and iodo, in which preferable one is chloro.

          Suitable "mono(or di or tri)halo(lower)alkyl" may include chloromethyl, dichloromethyl, trichloromethyl,  
10   bromomethyl, dibromomethyl, tribromomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1 or 2-chloroethyl, 1 or 2-bromoethyl, 1 or 2-fluoroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl and the like.

15           Suitable "protected carboxy" may include esterified carboxy such as lower alkoxy carbonyl [e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, pentyloxy carbonyl, hexyloxy carbonyl, etc.],  
          halo(lower)alkoxy carbonyl [e.g. (chloromethoxy) carbonyl,  
20   (2,2,2-trichloroethoxy) carbonyl, (2,2,2-trifluoroethoxy) carbonyl, (2-chloropropoxy) carbonyl, (1-fluoro-4-bromobutoxy) carbonyl, (4-chloropentyloxy) carbonyl, (6-chlorohexyloxy) carbonyl, etc.],

          higher alkoxy carbonyl [e.g. heptyloxy carbonyl,  
25   octyloxy carbonyl, 2-ethylhexyloxy carbonyl, nonyloxy carbonyl, decyloxy carbonyl, 3,7-dimethyloctyloxy carbonyl, undecyloxy carbonyl, dodecyloxy carbonyl, tridecyloxy carbonyl, tetradecyloxy carbonyl, pentadecyloxy carbonyl, 3-methyl-10-ethyl dodecyloxy carbonyl, hexadecyloxy carbonyl,  
30   heptadecyloxy carbonyl, octadecyloxy carbonyl, nonadecyloxy carbonyl, icosyloxy carbonyl, etc.],  
          aryloxy carbonyl [e.g. phenoxycarbonyl, naphthyloxy carbonyl, etc.],

          aryl(lower)alkoxy carbonyl which may have one or more  
35   (preferably 1 to 3) suitable substituent(s) such as

phenyl(lower)alkoxycarbonyl which may have nitro or lower alkoxy [e.g. benzyloxycarbonyl, phenethyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, etc.], and the like,

- 5 in which preferable one is lower alkoxy carbonyl and more preferable one is methoxycarbonyl, ethoxycarbonyl or tert-butoxycarbonyl.

Suitable "leaving group" may include hydroxy, reactive  
10 group derived from hydroxy and the like.

Suitable "reactive group derived from hydroxy" may include acid residue and the like.

Suitable "acid residue" may include halogen (e.g. fluoro, chloro, bromo, iodo), acyloxy (e.g. acetoxy,  
15 tosyloxy, mesyloxy, trifluoromethanesulfonyloxy, etc.) and the like.

Suitable example of "amino protective group" moiety may be common amino protective group such as substituted or  
20 unsubstituted lower alkanoyl [e.g. formyl, acetyl, propionyl, trifluoroacetyl, etc.], phthaloyl, lower alkoxy carbonyl [e.g. tert-butoxycarbonyl, tert-amyloxycarbonyl, etc.], substituted or unsubstituted aralkyloxycarbonyl [e.g. benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, etc.],  
25 substituted or unsubstituted arenesulfonyl [e.g. benzenesulfonyl, tosyl, etc.], nitrophenylsulfenyl, ar(lower)alkyl [e.g. trityl, benzyl, etc.], and the like, in which preferable one is tert-butoxycarbonyl.

30 Suitable salts of the object aminoalcohol derivative [I] are pharmaceutically acceptable salts and include conventional non-toxic salts such as an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], an organic acid addition salt [e.g.  
35 formate, acetate, trifluoroacetate, oxalate, maleate,

fumarate, tartrate, citrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc., an alkali metal salt [e.g. sodium salt, potassium salt, etc.] or the like.

5       The Processes 1 to 6 for preparing the object compounds of the present invention are explained in detail in the following.

Process 1

10       The object compound [I] or a salt thereof can be prepared by reacting a compound [II] with a compound [III] or a salt thereof.

Suitable salt of the compound [III] may be the same as those exemplified for the compound [I].

15       The reaction is preferably carried out in the presence of a base such as an alkali metal carbonate [e.g. sodium carbonate, potassium carbonate, etc.], an alkaline earth metal carbonate [e.g. magnesium carbonate, calcium carbonate, etc.], an alkali metal bicarbonate [e.g. sodium bicarbonate, 20 potassium bicarbonate, etc.], tri(lower)alkylamine [e.g. trimethylamine, triethylamine, etc.], picoline or the like.

The reaction is usually carried out in a conventional solvent, such as an alcohol [e.g. methanol, ethanol, propanol, isopropanol, etc.], diethyl ether, tetrahydrofuran, 25 dioxane, or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

30   Process 2

The object compound [Ib] or a salt thereof can be prepared by subjecting a compound [Ia] or a salt thereof to elimination reaction of the amino protective group.

Suitable salts of the compounds [Ia] and [Ib] may be 35 the same as those exemplified for the compound [I].

This reaction can be carried out in a similar manner to that of Example 11 mentioned below.

#### Process 3

5       The object compound [Ic] or a salt thereof can be prepared by reacting a compound [IV] or a salt thereof with a compound [V] or a salt thereof.

Suitable salts of the compounds [Ic], [IV] and [V] may be the same as those exemplified for the compound [I].

10       This reaction can be carried out in a similar manner to that of Example 15 mentioned below.

#### Process 4

15       The object compound [Ic] or a salt thereof can be prepared by reacting a compound [IV] or a salt thereof with a compound [VI] or a salt thereof.

Suitable salts of the compound [Ic], [IV] and [VI] may be the same as those exemplified for the compound [I].

20       This reaction can be carried out in a similar manner to that of Example 9 mentioned below.

#### Process 5

25       The object compound [Id] or a salt thereof can be prepared by reacting a compound [VII] or a salt thereof with a compound [V] or a salt thereof.

Suitable salts of the compounds [Id], [VII] and [V] may be the same as those exemplified for the compound [I].

This reaction can be carried out in a similar manner to that of Example 7 mentioned below.

30

#### Process 6

35       The object compound [Ig] or a salt thereof can be prepared by subjecting a compound [Ie] or a salt thereof to deesterification reaction followed by subjecting a compound [If] or a salt thereof to elimination reaction of the amino

protective group.

Suitable salts of the compound [Ig], [Ie] and [If] may be the same as those exemplified for the compound [I].

These reactions can be carried out in a similar manner  
5 to that of Example 18 mentioned below.

The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography,  
10 reprecipitation, or the like, and converted to the desired salt in conventional manners, if necessary.

It is to be noted that the compound [I] and the other compounds may include one or more stereoisomers due to asymmetric carbon atoms, and all of such isomers and mixture  
15 thereof are included within the scope of this invention.

It is further to be noted that isomerization or rearrangement of the object compound [I] may occur due to the effect of the light, acid base or the like, and the compound obtained as the result of said isomerization or  
20 rearrangement is also included within the scope of the present invention.

It is also to be noted that the solvating form of the compound [I] (e.g. hydrate, etc.) and any form of the crystal of the compound [I] are included within the scope of  
25 the present invention.

The object compound [I] or a salt thereof possesses gut sympathomimetic, anti-ulcerous, anti-pancreatitis, lipolytic, anti-urinary incontinence and anti-pollakiuria activities,  
30 and are useful for the treatment and/or prevention of gastro-intestinal disorders caused by smooth muscle contractions in human beings or animals, and more particularly for the treatment and/or prevention of spasm or hyperanakisia in case of irritable bowel syndrome,  
35 gastritis, gastric ulcer, duodenal ulcer, enteritis,



cholecystopathy, cholangitis, urinary calculus and the like;  
for the treatment and/or prevention of ulcer such as gastric  
ulcer, duodenal ulcer, peptic ulcer, ulcer causes by non  
steroidal anti-inflammatory drugs, or the like; for the  
5 treatment and/or prevention of dysuria or overactive bladder  
disorder such as pollakiuria, urinary incontinence, urge  
incontinence or the like in case of nervous pollakiuria,  
neurogenic bladder dysfunction, nocturia, unstable bladder,  
cystospasm, chronic cystitis, chronic prostatitis, prostatic  
10 hypertrophy or the like; for the treatment and/or prevention  
of pancreatitis, obesity, diabetes, glycosuria,  
hyperlipidemia, hypertension, atherosclerosis, glaucoma,  
melancholia, depression or the like; for the treatment  
and/or prevention of diseases as the result of insulin  
15 resistance (e.g. hypertension, hyperinsulinemia, etc.); for  
the treatment and/or prevention of neurogenetic  
inflammation; and for reducing a wasting condition, and the  
like.

Additionally,  $\beta_3$  adrenergic receptor agonists are known  
20 to lower triglyceride and cholesterol levels and to raise  
high density lipoprotein levels in mammals (US Patent No.  
5,451,677). Accordingly, the object compound [I] is useful  
in the treatment and/or prevention of conditions such as  
hyper-triglyceridaemia, hypercholesterolaemia and in  
25 lowering high density lipoprotein levels as well as in the  
treatment of atherosclerotic and cardiovascular diseases and  
related conditions.

Moreover, the object compound [I] is useful for  
30 inhibiting uterine contractions, preventing premature labor,  
and treating and preventing dysmenorrhea.

In order to show the usefulness of the compound [I] for  
the prophylactic and therapeutic treatment of above-  
35 mentioned disease in human being or animals, a

representative compound of the compound [I] was tested on the following pharmaceutical test.

#### Test

- 5        Effect on the increase in intravesical pressure induced by carbachol in anesthetized dog

#### Test compound

- 10        (1) 4'-[(2R)-2-[[ (2R)-2-Phenyl-2-hydroxyethyl]amino]-propyl]-3-methoxy-1,1'-biphenyl-4-carboxylic acid hydrochloride,  
          (2) 4'-[2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-ethyl]-2,3-dimethyl-1,1'-biphenyl-4-carboxylic acid hydrochloride,  
15        (3) 4'-[2-[[ (2R)-2-Hydroxy-2-(3-pyridyl)ethyl]amino]ethyl]-2-methyl-1,1'-biphenyl-4-carboxylic acid dihydrochloride,  
          (4) 4'-[(2R)-2-[[ (2R)-2-Hydroxy-2-(3-pyridyl)ethyl]amino]-propyl]-3-methoxy-1,1'-biphenyl-4-carboxylic acid  
20        dihydrochloride.

#### Test Method

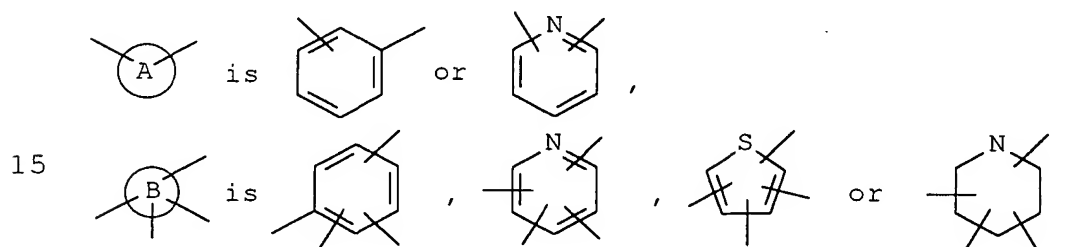
- Female Beagle dogs weighing 8.0-15.0 kg were fasted for 24 hours and maintained under halothane anesthesia. A 12F  
25        Foley catheter was lubricated with water soluble jelly, inserted into the urethral orifice and advanced approximately 10 cm until the balloon tip was placed well inside the bladder. The balloon was then inflated with 5 ml of room air and catheter slowly withdrawn just past the  
30        first resistance that is felt at the bladder neck. Urine was completely drained out through the catheter, and 30 ml of biological saline was infused. The catheter was connected to pressure transducer, and intravesical pressure (IVP) was continuously recorded. The test compound was  
35        administered intravenously at 30 minutes before the

administration of carbachol (1.8  $\mu\text{g/kg}$ ). Percent inhibition of IVP increase by test compound was calculated by dividing IVPa (IVP increase induced by carbachol after test compound administration) by IVPb (IVP increase induced by carbachol just before test compound administration).

### Test Results

Treatment	Percent inhibition of IVP increase
Test Compound (1) (0.032 mg/kg)	93
Test Compound (2) (0.032 mg/kg)	91
Test Compound (3) (0.032 mg/kg)	86
Test Compound (4) (0.032 mg/kg)	96

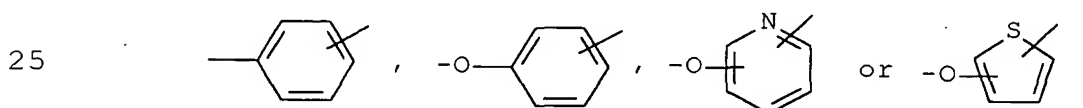
Preferred embodiments of the object compound [I] are as follows:



X is bond, -O-, -OCH<sub>2</sub>-, -S- or -N-<sub>R<sup>7</sup></sub> (in which R<sup>7</sup> is

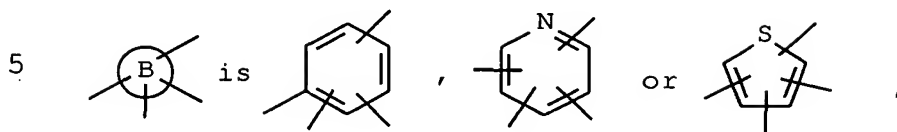
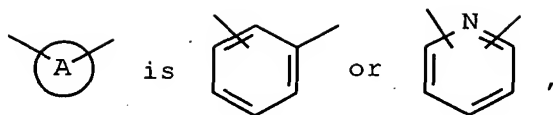
hydrogen or lower alkyl (more preferably C<sub>1</sub>-C<sub>4</sub> alkyl, most preferably methyl)),


Y is bond, -O-(CH<sub>2</sub>)<sub>n</sub>- (in which n is 1, 2, 3 or 4), -(CH<sub>2</sub>)<sub>m</sub>- (in which m is 1, 2, 3 or 4),



- Z is carboxy or lower alkoxycarbonyl (more preferably C<sub>1</sub>-C<sub>4</sub> alkoxycarbonyl, most preferably methoxycarbonyl, ethoxycarbonyl or tert-butoxycarbonyl),
- R<sup>1</sup> is hydrogen or halogen (more preferably chloro),
- 5 R<sup>2</sup> is hydrogen,
- R<sup>3</sup> is hydrogen or lower alkyl (more preferably C<sub>1</sub>-C<sub>4</sub> alkyl, most preferably methyl),
- R<sup>4</sup> is hydrogen,
- R<sup>5</sup> is halogen (more preferably chloro), hydroxy, lower alkyl
- 10 (more preferably C<sub>1</sub>-C<sub>6</sub>, most preferably methyl), lower alkoxy (more preferably C<sub>1</sub>-C<sub>6</sub> alkoxy, most preferably methoxy, ethoxy, propoxy, isopropoxy, butoxy or pentyloxy), hydroxy(lower)alkoxy (more preferably hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, most preferably 2-hydroxyethoxy),
- 15 mono(or di or tri)halo(lower)alkoxy (more preferably mono(or di or tri)halo(C<sub>1</sub>-C<sub>4</sub>)alkoxy, most preferably 2-fluoroethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, 3-fluoropropoxy or 3,3,3-trifluoropropoxy), lower alkoxy(lower)alkoxy (more preferably C<sub>1</sub>-C<sub>4</sub>
- 20 alkoxy(C<sub>1</sub>-C<sub>4</sub>)alkoxy, most preferably 2-methoxyethoxy), lower alkenyloxy (more preferably C<sub>2</sub>-C<sub>4</sub> alkenyl, most preferably allyloxy), cyclo(lower)alkyloxy (more preferably cyclo(C<sub>3</sub>-C<sub>6</sub>)alkyloxy, most preferably cyclohexyloxy), phenoxy or phenyl,
- 25 R<sup>6</sup> is hydrogen,
- R<sup>8</sup> is hydrogen or lower alkyl (more preferably C<sub>1</sub>-C<sub>4</sub> alkyl, most preferably methyl),
- R<sup>9</sup> is hydrogen or lower alkyl (more preferably C<sub>1</sub>-C<sub>4</sub> alkyl, most preferably methyl), and
- 30 i is 1 or 2.

More preferred embodiments of the object compound [I] are as follows:



X is bond, -O-, -OCH<sub>2</sub>-, -S- or -N- (in which R<sup>7</sup> is  


hydrogen or lower alkyl (more preferably C<sub>1</sub>-C<sub>4</sub> alkyl,  
 10 most preferably methyl)),

Y is bond, -O-(CH<sub>2</sub>)<sub>n</sub>- (in which n is 1 or 2) or -(CH<sub>2</sub>)<sub>m</sub>- (in  
 which m is 1 or 2),

Z is carboxy or lower alkoxy carbonyl (more preferably C<sub>1</sub>-C<sub>4</sub>  
 alkoxy carbonyl, most preferably methoxy carbonyl,

15 ethoxy carbonyl or tert-butoxy carbonyl),

R<sup>1</sup> is hydrogen or halogen (more preferably chloro),

R<sup>2</sup> is hydrogen,

R<sup>3</sup> is hydrogen or lower alkyl (more preferably C<sub>1</sub>-C<sub>4</sub> alkyl,  
 most preferably methyl),

20 R<sup>4</sup> is hydrogen,

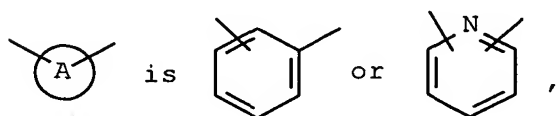
R<sup>5</sup> is hydrogen, halogen (more preferably chloro), hydroxy,  
 lower alkyl (more preferably C<sub>1</sub>-C<sub>6</sub>, most preferably  
 methyl), or lower alkoxy (more preferably C<sub>1</sub>-C<sub>6</sub> alkoxy,  
 most preferably methoxy),

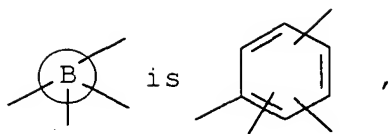
25 R<sup>6</sup> is hydrogen,

R<sup>8</sup> is hydrogen or lower alkyl (more preferably C<sub>1</sub>-C<sub>4</sub> alkyl,  
 most preferably methyl), and

i is 1.

30 Further more preferred embodiments of the compound [I]  
 are as follows:





X is bond,

5 Y is bond,

Z is carboxy or lower alkoxy carbonyl (more preferably C<sub>1</sub>-C<sub>4</sub> alkoxy carbonyl, most preferably methoxycarbonyl, ethoxycarbonyl or tert-butoxycarbonyl),

R<sup>1</sup> is hydrogen or halogen (more preferably chloro),

10 R<sup>2</sup> is hydrogen,

R<sup>3</sup> is hydrogen or lower alkyl (more preferably C<sub>1</sub>-C<sub>4</sub> alkyl, most preferably methyl),

R<sup>4</sup> is hydrogen,

15 R<sup>5</sup> is hydrogen (more preferably chloro), hydroxy, lower alkyl (more preferably C<sub>1</sub>-C<sub>4</sub> alkyl, most preferably methyl) or lower alkoxy (more preferably C<sub>1</sub>-C<sub>4</sub> alkoxy, most preferably methoxy or ethoxy),

R<sup>6</sup> is hydrogen,

20 R<sup>8</sup> is hydrogen or lower alkyl (more preferably C<sub>1</sub>-C<sub>4</sub> alkyl, most preferably methyl),

R<sup>9</sup> is hydrogen or lower alkyl (more preferably C<sub>1</sub>-C<sub>4</sub> alkyl, most preferably methyl), and

i is 1.

25 The following Preparations and Examples are given for the purpose of illustrating this invention.

#### Preparation 1

A solution of N-benzyl-2-(4-bromophenyl)ethanamine  
30 (13.5 g) in ethanol (270 ml) was added (2R)-2-(3-chlorophenyl)oxirane (8.63 g) and the solution was refluxed for 48 hours. After cooling to room temperature, the solvent was removed by evaporation and the residue was chromatographed on silica gel (eluent: hexane/ethyl acetate  
35 = 9/1) to give (1R)-2-[benzyl[2-(4-bromophenyl)ethyl]amino]-

1-(3-chlorophenyl)ethanol (18.6 g) as a colorless oil.

NMR (CDCl<sub>3</sub>,  $\delta$ ): 2.58 (1H, dd, J=10, 13Hz), 2.68-2.89  
 (5H, m), 3.56 (1H, d, J=13Hz), 3.92 (1H, d,  
 J=13Hz), 4.59 (1H, dd, J=3.4, 10Hz), 6.97 (2H, d,  
 J=8.3Hz), 7.21-7.40 (12H, m)  
 (+)ESI-MS (m/z): 444 and 446 (MH<sup>+</sup>)

### Preparation 2

To a solution of (1R)-2-[benzyl[2-(4-bromophenyl)ethyl]amino]-1-(3-chlorophenyl)ethanol (18.5 g) in N,N-dimethylformamide (40 ml) were successively added imidazole (3.96 g) and tert-butyldimethylsilyl chloride (7.52 g) and the solution was stirred at room temperature for 14 hours. The reaction mixture was quenched by the addition of water (100 ml) and extracted with ethyl acetate (100 ml x 1). The extract was washed with water (100 ml x 2), brine (100 ml x 1), and dried over magnesium sulfate. Filtration followed by evaporation gave a colorless oil, which was chromatographed on silica gel (eluent: hexane/ethyl acetate) to give (2R)-N-benzyl-N-[2-(4-bromophenyl)ethyl]-2-[[tert-butyl(dimethyl)silyl]oxy]-2-(3-chlorophenyl)ethanamine (21.0 g) as a colorless oil.

NMR (CDCl<sub>3</sub>,  $\delta$ ): 0.15 (6H, s), 1.01 (9H, s), 2.72-2.82  
 (5H, m), 2.92 (1H, dd, J=5.9, 13Hz), 3.75 (1H, d,  
 J=13.7Hz), 3.86 (1H, d, J=13.7Hz), 4.71 (1H, t-like, J=6.2Hz), 7.01 (2H, d, J=8.3Hz), 7.26-7.47  
 (9H, m), 7.48 (2H, d, J=8.3Hz)  
 (+)ESI-MS (m/z): 558 and 560 (MH<sup>+</sup>)

### Preparation 3

To a solution of tert-butyl [2-(4-bromophenyl)ethyl][(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate (500 mg) in 1,2-dimethoxyethane (6 ml) was added 5-formyl-2-thiopheneboronic acid (206 mg), tetrakis(triphenylphosphine)palladium (63 mg) and aqueous

solution of sodium carbonate (2M, 1.0 ml), and the mixture was stirred at 80°C for 7 hours under nitrogen. The mixture was diluted with ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium

5 sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 3/1) to give tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-[4-(5-formyl-2-thienyl)phenyl]ethyl]carbamate (187 mg).

10 (+)ESI-MS (m/z): 508 (M+Na)<sup>+</sup>

#### Preparation 4

To a suspension of tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-(4-hydroxyphenyl)ethyl]carbamate (710 mg),  
15 4-[[tert-butyl(dimethyl)silyl]oxy]phenylboronic acid (457 mg), triethylamine (1.26 ml) and powdered 4Å molecular sieves (700 mg) in dichloromethane (18 ml) was added copper(II) acetate (330 mg), and the mixture was stirred at room temperature for 18 hours under ambient atmosphere. The  
20 resulting slurry was filtered off, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give tert-butyl [2-[4-[4-[[tert-butyl(dimethyl)silyl]oxy]phenoxy]phenyl]ethyl][(2R)-2-(3-chlorophenyl)-2-  
25 hydroxyethyl]carbamate (600 mg).

(-)ESI-MS (m/z): 569 (M-H)<sup>-</sup>

#### Preparation 5

The following compounds were obtained according to a  
30 similar manner to that of Preparation 4.

(1) tert-Butyl [2-[4-[4-[[tert-butyl(dimethyl)silyl]oxy]phenyl]amino]phenyl]ethyl][(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate

35 (+)ESI-MS (m/z): 597 (M+H)<sup>+</sup>



(2) tert-Butyl [2-[4-[[4-[[tert-butyl(dimethyl)silyl]oxy]-phenyl](methyl)amino]phenyl]ethyl][(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate

5 (+)ESI-MS (m/z): 611 (M+H)<sup>+</sup>

#### Preparation 6

To a solution of tert-butyl [2-(4-aminophenyl)-ethyl][(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate  
 10 (1.75 g) and formaldehyde (37% w/w solution in water, 390  $\mu$ l) in 1,2-dichloroethane (20 ml) was added sodium triacetoxyborohydride (1.23 g), and the mixture was stirred at room temperature for 18 hours under nitrogen atmosphere. The resulting mixture was poured into a mixture of 1N sodium  
 15 hydroxide and chloroform, and the mixture was stirred for 20 minutes. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give tert-  
 20 butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-[4-(methylamino)phenyl]ethyl]carbamate (550 mg).

(+)ESI-MS (m/z): 405 (M+H)<sup>+</sup>

#### Preparation 7

25 To a suspension of 2-[4-[(4-methoxyphenyl)thio]phenyl]-ethanamine (6.3 g) in methanol (45 ml) and tetrahydrofuran (10 ml) was added ethyl trifluoroacetate (2.89 ml), and the mixture was stirred at room temperature for 1 hour. The mixture was evaporated under reduced pressure. The residue  
 30 was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give 2,2,2-trifluoro-N-[2-[4-[(4-methoxyphenyl)thio]phenyl]ethyl]acetamide (3.95 g).

(+)ESI-MS (m/z): 378 (M+Na)<sup>+</sup>

#### 35 Preparation 8

Under nitrogen at 4°C, to a solution of 2,2,2-trifluoro-N-[2-[4-[(4-methoxyphenyl)thio]phenyl]ethyl]-acetamide (1.5 g) in dichloromethane (15 ml) was added 1M boron tribromide in dichloromethane (10.5 ml), and the  
5 mixture was stirred at room temperature for 15 hours. The mixture was evaporated under reduced pressure. The residue was dissolved in a mixture of dichloromethane and saturated aqueous sodium bicarbonate. After separation, the organic layer was dried over magnesium sulfate and evaporated under  
10 reduced pressure to give 2,2,2-trifluoro-N-[2-[4-[(4-hydroxyphenyl)thio]phenyl]ethyl]acetamide (1.42 g).

(+)ESI-MS (m/z): 364 (M+Na)<sup>+</sup>

#### Preparation 9

15 To a solution of 2,2,2-trifluoro-N-[2-[4-[(4-hydroxyphenyl)thio]phenyl]ethyl]acetamide (480 mg) in methanol (5.0 ml) was added 1N sodium hydroxide solution (2.8 ml). The mixture was refluxed for 12 hours. The mixture was evaporated under reduced pressure. The residue  
20 was dissolved in a mixture of dichloromethane (40 ml), 1N hydrochloric acid solution (2.0 ml) and water (15 ml). After separation, the organic layer was dried over magnesium sulfate and evaporated under reduced pressure to give 4-[[4-(2-aminoethyl)phenyl]thio]phenol (300 mg).

25 (-)ESI-MS (m/z): 244 (M-H)<sup>-</sup>

#### Preparation 10

4-[[4-(2-Aminoethyl)phenyl]thio]phenol (295 mg) and (2R)-2-(3-chlorophenyl)oxirane (186 mg) in ethanol (3.5 ml)  
30 was refluxed for 6 hours. The mixture was evaporated. The residue was purified by column chromatography on silica gel (chloroform/methanol = 100/3) to give 4-[[4-[2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]thio]phenol (155 mg).

35 (+)ESI-MS (m/z): 400 (M+H)<sup>+</sup>

The object compound above was protected at the imino group in a conventional manner to give tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-[4-[(4-hydroxyphenyl)-thio]phenyl]ethyl]carbamate (200 mg).

(+)ESI-MS (m/z): 500 (M+H)<sup>+</sup>

#### Preparation 11

The following compounds were obtained according to a similar manner to that of Preparation 10.

(1) (1R)-2-[[2-(4-Bromophenyl)ethyl]amino]-1-(3-chlorophenyl)ethanol

(+)ESI-MS (m/z): 354 (M+H)<sup>+</sup>

(2) tert-Butyl [2-(4-bromophenyl)ethyl][(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate

(+)ESI-MS (m/z): 454 (M+H)<sup>+</sup>

#### Example 1

To a solution of tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-[4-(5-formyl-2-thienyl)phenyl]ethyl]carbamate (180 mg) in acetonitrile (2 ml) and pH 4 buffer solution (sodium dihydrogenphosphate) (1 ml) was added 30% hydrogen peroxide solution (30  $\mu$ l) and 80% sodium chlorite (67 mg) below 10°C. The reaction mixture was stirred at 50°C for 3 hours. The mixture was diluted with ethyl acetate, washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to give 5-[4-[2-[(tert-butoxycarbonyl][(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-2-thiophenecarboxylic acid (160 mg).

(-)ESI-MS (m/z): 500 (M-H)<sup>-</sup>

#### Example 2

The following compounds were obtained according to a similar manner to that of Example 4.

- (1) 5-[4-[2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenyl]-2-thiophenecarboxylic acid hydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 3.00-3.25 (6H, m), 4.95-4.99 (1H, m), 6.34 (1H, br), 7.33-7.47 (6H, m), 7.55 (1H, d, J=3.9Hz), 7.70-7.81 (3H, m), 9.05 (1H, br)  
(-)ESI-MS (m/z): 400 (M-HCl-H)<sup>-</sup>
- (2) [4-[[4-[2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenyl]amino]phenoxy]acetic acid hydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 2.84-3.30 (6H, m), 4.39 (1H, br), 4.59 (2H, s), 4.97-5.03 (1H, m), 6.37 (1H, br), 6.80-7.07 (8H, m), 7.34-7.48 (4H, m), 8.85 (1H, br), 9.11 (1H, br)  
(-)ESI-MS (m/z): 439 (M-HCl-H)<sup>-</sup>
- (3) [4-[[4-[2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenyl](methyl)amino]phenoxy]acetic acid hydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 2.85-3.23 (6H, m), 3.17 (3H, s), 3.89-4.15 (1H, br), 4.65 (2H, s), 4.98-5.02 (1H, m), 6.68-7.08 (8H, m), 7.34-7.46 (4H, m), 8.86 (1H, br), 9.14 (1H, br)  
(-)ESI-MS (m/z): 453 (M-HCl-H)<sup>-</sup>
- (4) [4-[[4-[2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenyl]thio]phenoxy]acetic acid hydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 2.94-3.33 (6H, m), 4.70 (2H, s), 4.97-5.01 (1H, m), 6.34 (1H, br), 6.96 (2H, d, J=8.7Hz), 7.02-7.23 (4H, m), 7.33-7.45 (6H, m),

8.97-9.18 (1H, br)

(-)ESI-MS (m/z): 456 (M-HCl-H)<sup>-</sup>

### Example 3

5        To a solution of tert-butyl [2-[4-[4-[[tert-butyl(dimethyl)silyl]oxy]phenoxy]phenyl]ethyl][(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate (370 mg) in tetrahydrofuran (4.0 ml) was added 1M tetrabutylammonium fluoride in tetrahydrofuran (1.2 ml), and the mixture was  
10        stirred at room temperature for 1 hour. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to give a phenol product. To a solution of the product and  
15        potassium carbonate (94 mg) in N,N-dimethylformamide (4.0 ml) was added tert-butyl bromoacetate (133 mg), and the mixture was stirred at room temperature for 5 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine,  
20        dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give tert-butyl [4-[4-[2-[(tert-butoxycarbonyl][(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenoxy]phenoxy]-  
25        acetate (360 mg).

(-)ESI-MS (m/z): 597 (M-H)<sup>-</sup>

### Example 4

30        A solution of tert-butyl [4-[4-[2-[(tert-butoxycarbonyl][(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenoxy]phenoxy]acetate (305 mg) and 4N hydrochloride in 1,4-dioxane (5.0 ml) was stirred at room temperature for 24 hours. The resulting solid was collected by filtration and dried to give [4-[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenoxy]phenoxy]-  
35        acetate (360 mg).

acetic acid hydrochloride (220 mg) as a white solid.

NMR (DMSO- $d_6$ ,  $\delta$ ): 2.95-3.33 (6H, m), 4.65 (2H, s),  
 4.99-5.04 (1H, m), 6.35 (1H, br), 6.83-7.00 (6H,  
 m), 7.23 (9H, d,  $J=8.5\text{Hz}$ ), 7.39-7.47 (4H, m),  
 8.98-9.12 (1H, br)  
 (+)ESI-MS ( $m/z$ ): 442 ( $M\text{-HCl}+H$ )<sup>+</sup>

#### Example 5

To a suspension of tert-butyl [(2R)-2-(3-chlorophenyl)-  
 2-hydroxyethyl][2-(4-hydroxyphenyl)ethyl]carbamate (550 mg),  
 (4-methoxycarbonylphenyl)boronic acid (300 mg),  
 triethylamine (1.0 ml) and powdered 4Å molecular sieves (600  
 mg) in dichloromethane (8 ml) was added copper(II) acetate  
 (255 mg), and the mixture was stirred at room temperature  
 for 18 hours under ambient atmosphere. The resulting slurry  
 was filtered off, and the filtrate was evaporated under  
 reduced pressure. The residue was purified by column  
 chromatography on silica gel (hexane/ethyl acetate = 2/1) to  
 give methyl 4-[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-  
 chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenoxy]benzoate  
 (185 mg).

(+)ESI-MS ( $m/z$ ): 526 ( $M+H$ )<sup>+</sup>

#### Example 6

To a solution of methyl 4-[4-[2-[(tert-  
 butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-  
 hydroxyethyl]amino]ethyl]phenoxy]benzoate (183 mg) in  
 ethanol (1.2 ml) was added 1N aqueous sodium hydroxide  
 solution (0.6 ml), and the mixture was stirred at 40°C for 3  
 hours. The solvent was removed by evaporation, and the  
 aqueous solution was acidified with 1N aqueous hydrochloride  
 solution and extracted with ethyl acetate (30 ml x 2). The  
 combined organic layers were washed with water and brine,  
 dried over magnesium sulfate and evaporated under reduced  
 pressure to give a benzoic acid product. To a solution of

the product in tetrahydrofuran (2.0 ml) was added 4N hydrochloride in 1,4-dioxane (1.0 ml), and the mixture was stirred at room temperature for 12 hours. The resulting solid was collected by filtration and dried to give 4-[4-[2-  
 5 [[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-phenoxy]benzoic acid hydrochloride (127 mg).

NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 3.00-3.28 (6H, m), 4.99-5.04 (1H, m), 6.35 (1H, br), 6.97-7.12 (4H, m), 7.32-7.48 (6H, m), 7.90-7.98 (2H, m), 9.03-9.35 (1H, br)

10 (-)ESI-MS (m/z): 410 (M-HCl-H)<sup>-</sup>

#### Example 7

To a solution of tert-butyl [2-(4-bromophenyl)ethyl]-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate (400 mg)  
 15 in 1,2-dimethoxyethane (6 ml) was added (4-methoxycarbonyl-2-methylphenyl)boronic acid (171 mg), tetrakis(triphenylphosphine)palladium (55 mg) and aqueous solution of sodium carbonate (2M, 0.92 ml), and the mixture was stirred at 80°C for 2 hours under nitrogen. The mixture  
 20 was diluted with ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give methyl 4'-[2-[(tert-  
 25 butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino]ethyl]-2-methyl-1,1'-biphenyl-4-carboxylate (320 mg).

(+)ESI-MS (m/z): 524 (M+H)<sup>+</sup>

#### Example 8

30 The following compounds were obtained according to a similar manner to that of Example 6.

(1) 5-Chloro-6-[4-[2-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenoxy]nicotinic acid  
 35 hydrochloride

NMR (DMSO- $d_6$ ,  $\delta$ ): 3.04-3.32 (6H, m), 5.03-5.07 (1H, m),  
 5.14 (1H, br), 7.18 (2H, d,  $J=8.5\text{Hz}$ ), 7.33-7.48  
 (6H, m), 8.38 (1H, d,  $J=2.0\text{Hz}$ ), 8.54 (1H, d,  
 $J=2.0\text{Hz}$ ), 9.00 (1H, br), 9.35 (1H, br)

5 (-)ESI-MS ( $m/z$ ): 445 ( $M-\text{HCl}-\text{H}$ )<sup>-</sup>

(2) 4'-[2-[[2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-  
 ethyl]-2-methyl-1,1'-biphenyl-4-carboxylic acid  
 hydrochloride

10 NMR (DMSO- $d_6$ ,  $\delta$ ): 2.28 (1H, s), 3.01-3.27 (6H, m),  
 5.00-5.04 (1H, m), 6.36 (1H, br), 7.28-7.48 (9H,  
 m), 7.79-7.90 (2H, m), 9.02 (1H, br)

(-)ESI-MS ( $m/z$ ): 408 ( $M-\text{HCl}-\text{H}$ )<sup>-</sup>

#### 15 Example 9

To a solution of tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-(4-hydroxyphenyl)ethyl]carbamate (600 mg) and potassium carbonate (254 mg) in dimethylsulfoxide (6.0 ml) was added methyl 5,6-dichloro-3-pyridinecarboxylate (347  
 20 mg), and the mixture was stirred at room temperature for 12 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column  
 25 chromatography on silica gel (hexane/ethyl acetate = 2/1) to give methyl 6-[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenoxy]-5-chloronicotinate (770 mg).

(+)ESI-MS ( $m/z$ ): 561 ( $M+\text{H}$ )<sup>+</sup>

30

#### Example 10

Under nitrogen at 5°C, to a solution of tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-(4-hydroxyphenyl)ethyl]carbamate (1.5 g), ethyl [3-(  
 35 (hydroxymethyl)phenoxy]acetate (885 mg) and triphenyl



phosphine (1.1 g) in tetrahydrofuran (30 ml) was added diethyl azodicarboxylate (0.66 ml). The mixture was stirred at room temperature for 12 hours and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give ethyl [3-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenoxy]methyl]-phenoxy]acetate (1.04 g).

(+)ESI-MS (m/z): 585 (M+H)<sup>+</sup>

10

#### Example 11

To a solution of ethyl [3-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenoxy]methyl]phenoxy]acetate (1.0 g) in tetrahydrofuran (5.0 ml) was added 4N hydrochloride in dioxane (4.3 ml). The mixture was stirred at room temperature for 8 hours and evaporated under reduced pressure. The residue was diluted with ethyl acetate and saturated sodium bicarbonate solution. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (methanol/chloroform = 1/20) to give ethyl [3-[[4-[2-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenoxy]-methyl]phenoxy]acetate (632 mg).

15

20

25

(+)ESI-MS (m/z): 484 (M+H)<sup>+</sup>

The object compound above was hydrolyzed in a conventional manner to give sodium [3-[[4-[2-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenoxy]methyl]-phenoxy]acetate (492 mg).

30

NMR (DMSO-d<sub>6</sub>, δ): 2.56-2.73 (6H, m), 4.09 (2H, s), 4.58-4.64 (1H, m), 4.98 (2H, s), 6.72-6.77 (1H, m), 6.85-6.91 (4H, m), 7.08 (2H, d, J=8.5Hz), 7.17-7.26 (4H, m), 7.38 (1H, s)

35

(-)ESI-MS (m/z): 454 (M-Na-H)<sup>-</sup>

### Example 12

The following compounds were obtained according to a similar manner to that of Example 3.

(1) tert-Butyl [4-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]amino]-phenoxy]acetate

(+)ESI-MS (m/z): 597 (M+H)<sup>+</sup>

(2) tert-Butyl [4-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-(methyl)amino]phenoxy]acetate

(+)ESI-MS (m/z): 611 (M+H)<sup>+</sup>

### Example 13

To a solution of tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-[4-[(4-hydroxyphenyl)thio]phenyl]ethyl]-carbamate (195 mg) and potassium carbonate (59 mg) in N,N-dimethylformamide (3 ml) was added tert-butyl bromoacetate (84 mg), and the mixture was stirred at room temperature for 3 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 3/1) to give tert-butyl [4-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]thio]-phenoxy]acetate (168 mg).

(+)ESI-MS (m/z): 636 (M+Na)<sup>+</sup>

### Preparation 12

To a solution of 4-bromo-2-fluorobenzoate (1.5 g) in N,N-dimethylformamide (30 ml) was added bis(pinacolato)-

diboron (1.8 g), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloridedichloromethane complex (1:1) (263 mg) and potassium acetate (1.9 g), and the mixture was stirred at 100°C for 18 hours under nitrogen. The mixture  
5 was diluted with ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 5/1) to give methyl 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-  
10 dioxaborolan-2-yl)benzoate (350 mg).

(+)ESI-MS (m/z): 303 (M+Na)<sup>+</sup>

#### Preparation 13

To a solution of methyl 4-bromo-2-methoxybenzoate (2.0  
15 g) in 1,4-dioxane (40 ml) was added bis(pinacolato)diboron (2.07 g), dichlorobis(triphenylphosphine)palladium(II) (286 mg) and potassium acetate (2.4 g), and the mixture was stirred at 95°C for 10 hours under nitrogen. The mixture  
20 was diluted with ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 3/1) to give methyl 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-  
dioxaborolan-2-yl)benzoate (2.0 g).

25 (+)ESI-MS (m/z): 293 (M+H)<sup>+</sup>

#### Preparation 14

To a suspension of methyl 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (2.0 g) in  
30 acetone (70 ml) and water (70 ml) was added ammonium acetate (1.11 g) and sodium periodate (3.08 g), and the mixture was stirred at room temperature for 15 hours. The solvent was evaporated and the residue was diluted with ethyl acetate. The organic layer was separated, washed with water and brine,  
35 dried over magnesium sulfate and evaporated under reduced

pressure to give [3-methoxy-4-(methoxycarbonyl)phenyl]-boronic acid (1.4 g).

(+)ESI-MS (m/z): 209 (M-H)<sup>-</sup>

#### 5 Preparation 15

The following compounds were obtained according to a similar manner to that of Preparation 14.

(1) [3-Fluoro-4-(methoxycarbonyl)phenyl]boronic acid

10 (+)ESI-MS (m/z): 197 (M-H)<sup>-</sup>

(2) [2-Chloro-4-(methoxycarbonyl)phenyl]boronic acid

(+)ESI-MS (m/z): 213 (M-H)<sup>-</sup>

15 (3) [4-(Ethoxycarbonyl)-2-methoxyphenyl]boronic acid

(+)ESI-MS (m/z): 223 (M-H)<sup>-</sup>

#### Preparation 16

To a solution of ethyl 3-methoxy-4-[[trifluoromethyl)-  
20 sulfonyl]oxy]benzoate (1.52 g) in 1,4-dioxane (35 ml) was added bis(pinacolato)diboron (1.18 g), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloridedichloromethane complex (1:1) (309 mg) and potassium acetate (1.36 g), and the mixture was stirred at 100°C for 10 hours under nitrogen.  
25 The mixture was diluted with ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 5/1) to give ethyl 3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-  
30 dioxaborolan-2-yl)benzoate (700 mg).

(+)ESI-MS (m/z): 293 (M+H)<sup>+</sup>

#### Preparation 17

The following compound was obtained according to a  
35 similar manner to that of Preparation 16.

Methyl 3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

(+)ESI-MS (m/z): 297 (M+H)<sup>+</sup>

5

#### Preparation 18

To a solution of tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-(4-hydroxyphenyl)ethyl]carbamate (5.0 g) and 2,6-lutidine (2.97 ml) in dichloromethane (75 ml) was added  
 10 trifluoromethanesulfonic anhydride (2.36 ml) dropwise at -70°C under nitrogen and the mixture was stirred at -70°C for 30 minutes. The mixture was allowed to warm to room temperature and evaporated under reduced pressure. The residue was partitioned between ethyl acetate and water.  
 15 The organic layer was separated, washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give 4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-  
 20 amino]ethyl]phenyl trifluoromethanesulfonate (6.6 g).

(+)ESI-MS (m/z): 546 (M+Na)<sup>+</sup>

#### Preparation 19

25 To a solution of methyl 4-bromo-2-methylbenzoate (6.9 g) in 1,4-dioxane (150 ml) was added bis(pinacolato)diboron (8.03 g), dichlorobis(triphenylphosphine)palladium(II) (1.69 g) and potassium acetate (8.87 g), and the mixture was stirred at 95°C for 2 hours under nitrogen. The mixture was  
 30 diluted with ethyl acetate and water. The organic layer was separated, washed with 1N hydrochloric acid and brine, dried over magnesium sulfate and evaporated. To a suspension of the crude product (11 g) in acetone (200 ml) and water (200 ml) was added ammonium acetate (5.1 g) and sodium periodate  
 35 (14.1 g), and the mixture was stirred at room temperature

for 6 hours. The solvent was evaporated, and the mixture was diluted with ethyl acetate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The resultant solid was triturated with diisopropyl ether to give [3-methyl-4-(methoxycarbonyl)phenyl]boronic acid (2.65 g).

(+)ESI-MS (m/z): 193 (M-H)<sup>-</sup>

#### 10 Preparation 20

To a solution of 4-hydroxy-2,3-dimethylbenzaldehyde (1.9 g) and pyridine (5.12 ml) in dichloromethane (40 ml) was added trifluoromethanesulfonic anhydride (2.34 ml) under nitrogen and the mixture was stirred at room temperature for 30 minutes and evaporated under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure to give 4-formyl-2,3-dimethylphenyl trifluoromethanesulfonate (2.7 g).

(+)ESI-MS (m/z): 281 (M-H)<sup>-</sup>

#### Preparation 21

To a solution of 4-formyl-2,3-dimethylphenyl trifluoromethanesulfonate (2.5 g) in 1,4-dioxane (50 ml) was added bis(pinacolato)diboron (2.47 g), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloridedichloromethane complex (1:1) (1.09 g) and potassium acetate (2.61 g), and the mixture was stirred at 90°C for 5 hours under nitrogen. The mixture was diluted with ethyl acetate and water. The organic layer was separated, washed with 1N hydrochloric acid and brine, dried over magnesium sulfate and evaporated. To a suspension of the crude product in acetone (80 ml) and water (80 ml) was added ammonium acetate (1.4 g) and sodium periodate (3.95 g), and the mixture was stirred at room

temperature for 6 hours. The solvent was evaporated, and the mixture was diluted with ethyl acetate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure.

- 5 The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 1/1) to give (4-formyl-2,3-dimethylphenyl)boronic acid (560 mg).

(+)ESI-MS (m/z): 177 (M-H)<sup>-</sup>

10 Preparation 22

- To a solution of N-benzyl-N-[2-(4-bromophenyl)ethyl]-carbamate (1.3 g) in 1,2-dimethoxyethane (20 ml) was added [4-(methoxycarbonyl)-2-methylphenyl]boronic acid (792 mg), tetrakis(triphenylphosphine)palladium (360 mg) and aqueous  
15 solution of sodium carbonate (2M, 4.1 ml), and the mixture was stirred at 80°C for 2 hours under nitrogen. The mixture was diluted with ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue  
20 was purified by column chromatography on silica gel (hexane/ethyl acetate = 3/1) to give methyl 4'-[2-[[[(benzyloxy)carbonyl]amino]ethyl]-2-methyl-1,1'-biphenyl-4-carboxylate (660 mg).

(+)ESI-MS (m/z): 426 (M+Na)<sup>+</sup>

25

Preparation 23

- To a solution of 2,2,2-trifluoro-N-[3-(4-iodophenyl)-propyl]acetamide (2.5 g) in 1,2-dimethoxyethane (15 ml) was added [4-(methoxycarbonyl)phenyl]boronic acid (1.51 g),  
30 tetrakis(triphenylphosphine)palladium (809 mg) and aqueous solution of sodium carbonate (2M, 7 ml), and the mixture was stirred at 75°C for 10 hours under nitrogen. The mixture was diluted with ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium  
35 sulfate and evaporated. The residue was purified by column

chromatography on silica gel (hexane/ethyl acetate = 2/1) to give methyl 4'-[3-[(trifluoroacetyl)amino]propyl]-1,1'-biphenyl-4-carboxylate (920 mg).

MS (m/z): 366 (M+H)

5

#### Preparation 24

The following compound was obtained according to a similar manner to that of Preparation 23.

10 Ethyl 4'-[2-[[ (benzyloxy)carbonyl]amino]ethyl]-2-methoxy-1,1'-biphenyl-4-carboxylate

MS (m/z): 434 (M+H)

#### Preparation 25

15 A mixture of methyl 4'-[3-[(trifluoroacetyl)amino]-propyl]-1,1'-biphenyl-4-carboxylate (920 mg), 4N hydrochloride in ethanol (2 ml) and ethanol (2 ml) was refluxed for 18 hours. The mixture was evaporated in vacuo. The residue was diluted with ethyl acetate and saturated  
20 aqueous sodium bicarbonate solution. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (chloroform:methanol = 100:1) to give ethyl 4'-(3-aminopropyl)-1,1'-biphenyl-4-carboxylate  
25 (200 mg) as a colorless foam.

MS (m/z): 284 (M+H)

#### Preparation 26

To a solution of ethyl (1R)-1-(6-chloro-3-pyridyl)-2-  
30 [[3-(4-iodophenyl)propyl]amino]ethanol (2.0 g) in tetrahydrofuran (3.5 ml) was added di-tert-butyl dicarbonate (53 mg), and the mixture was stirred at room temperature for 2 hours. The mixture was evaporated. The residue was purified by column chromatography on silica gel  
35 (hexane/ethyl acetate = 2/1) to give tert-butyl [(2R)-2-(6-



chloro-3-pyridyl)-2-hydroxyethyl][3-(4-iodophenyl)propyl]-  
carbamate (2.62 g).

MS (m/z): 517 (M+H)

5 Preparation 27

To a solution of 2,2,2-trifluoro-N-[(1R)-2-(4-  
iodophenyl)-1-methylethyl]acetamide in dioxane (10 ml) was  
added 1N sodium hydroxide (12 ml) and the mixture was  
stirred for 1 hour at room temperature. The mixture was  
10 diluted with ethyl acetate and water. The organic layer was  
separated, washed with brine, dried over magnesium sulfate  
and evaporated to give [(1R)-2-(4-iodophenyl)-1-  
methylethyl]amine (2.34 g) as a yellow oil.

MS (m/z): 262 (M+H)

15

Preparation 28

A solution of [(1R)-2-(4-iodophenyl)-1-methylethyl]-  
amine (1.0 g) and 2-chloro-5-[(2R)-2-oxiranyl]pyridine (298  
mg) in ethanol (10 ml) was refluxed for 18 hours. The  
20 mixture was evaporated in vacuo. To the residue was added  
di-tert-butyl dicarbonate (418 mg) and tetrahydrofuran (10  
ml) and the mixture was stirred at room temperature for 2  
hours and then evaporated. The residue was purified by  
column chromatography on silica gel (hexane/ethyl acetate =  
25 1/1) to give tert-butyl [(2R)-2-(6-chloro-3-pyridyl)-2-  
hydroxyethyl][(1R)-2-(4-iodophenyl)-1-methylethyl]carbamate  
(700 mg).

MS (m/z): 517 (M+H)

30 Preparation 29

The following compound was obtained according to a  
similar manner to that of Preparation 28.

tert-Butyl [(2R)-2-(6-chloro-3-pyridyl)-2-  
35 hydroxyethyl][2-(4-hydroxyphenyl)ethyl]carbamate

MS (m/z): 393 (M+H)

### Preparation 30

Under nitrogen at -60°C, to a solution of tert-butyl  
5 [2-(4-hydroxyphenyl)ethyl][(2R)-2-hydroxy-2-(3-pyridyl)-  
ethyl]carbamate (570 mg) and 2,6-lutidine (0.22 ml) in  
dichloromethane (10 ml) was added trifluoromethanesulfonic  
anhydride (0.28 ml), and the mixture was stirred at the same  
temperature for 1 hour. The resulting mixture was poured  
10 into aqueous ammonia and the aqueous mixture was extracted  
with ethyl acetate. The organic layer was washed  
successively with 1N hydrochloric acid, water, saturated  
aqueous sodium bicarbonate and brine, dried over anhydrous  
magnesium sulfate and evaporated under reduced pressure.  
15 The residue was purified by column chromatography on silica  
gel (hexane/ethyl acetate = 1:1) to give 4-[2-[(tert-  
butoxycarbonyl][(2R)-2-hydroxy-2-(3-pyridyl)ethyl]amino]-  
ethyl]phenyl trifluoromethanesulfonate (640 mg) as a  
colorless foam.

20 MS (m/z): 491 (M+H)

### Preparation 31

The following compound was obtained according to a  
similar manner to that of Preparation 30.

25

4-[2-[(tert-Butoxycarbonyl][(2R)-2-hydroxy-2-(3-  
chlorophenyl)ethyl]amino]propyl]phenyl  
trifluoromethanesulfonate

MS (m/z): 538 (M+H)

30

### Preparation 32

To a solution of 2,2,2-trifluoro-N-[(1R)-1-methyl-2-  
phenylethyl]acetamide (3.75 g) in acetic acid (32 ml) -  
water (6.5 ml) - sulfuric acid (0.97 ml) were added iodine  
35 (1.65 g) and periodic acid dihydrate (740 mg) at room

temperature, and the mixture was heated to 60 - 80°C for 5 hours. After being allowed to cool to room temperature, the mixture was partitioned between hexane/ethyl acetate and water. The organic layer was separated, washed successively  
 5 with water, sodium sulfite solution, water and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated and the residue was recrystallized from diisopropyl ether (44 ml) to give 2,2,2-trifluoro-N-[(1R)-2-(4-iodophenyl)-1-methylethyl]acetamide (2.15 g) as a  
 10 colorless needle.

NMR (CDCl<sub>3</sub>, δ): 1.21 (3H, d, J=7Hz), 2.74 (1H, dd, J=14, 7Hz), 2.85 (1H, dd, J=14, 6Hz), 4.26 (1H, m), 6.04 (1H, br s), 6.92 (2H, d, J=8Hz), 7.65 (2H, d, J=8Hz)

15 (+)ESI-MS (m/z): 380 (M+Na)<sup>+</sup>

### Preparation 33

The following compound was obtained according to a similar manner to that of Preparation 32.

20

2,2,2-Trifluoro-N-[3-(4-iodophenyl)propyl]acetamide

NMR (CDCl<sub>3</sub>, δ): 1.90 (2H, quintet, J=7Hz), 2.62 (2H, t, J=7Hz), 3.38 (2H, q, J=7Hz), 6.26 (1H, br s), 6.93 (2H, d, J=8Hz), 7.62 (2H, d, J=8Hz)

25 (+)ESI-MS (m/z): 380 (M+Na)<sup>+</sup>

### Preparation 34

To a mixture of 3-(4-hydroxyphenyl)propanoic acid (15.0 g), (1R)-2-amino-1-(3-chlorophenyl)ethanol hydrochloride  
 30 (18.8 g), and 1-hydroxybenzotriazole (14.6 g) in N,N-dimethylformamide (100 ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (26.0 g), and the mixture was stirred at room temperature for 3 hours. The mixture was partitioned between ethyl acetate  
 35 and water. The organic layer was separated, washed

successively with sodium bicarbonate solution and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to give  
5 N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-3-(4-hydroxyphenyl)propanamide (11.61 g) as a white amorphous powder.

MS (m/z): 320 (M+H)

10 Preparation 35

To a solution of N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-3-(4-hydroxyphenyl)propanamide (11.61 g) in tetrahydrofuran (70 ml) was added borane-methyl sulfide complex (10M, 11.9 ml) at 0°C, and the mixture was heated to  
15 80°C for 1 hour. After being allowed to cool to room temperature, the mixture was added 2N hydrochloric acid (20 ml) at 0°C. The mixture was heated to 80°C for 1 hour. After being allowed to cool to room temperature, the mixture was added 1N sodium hydroxide (40 ml) and di-tert-butyl  
20 dicarbonate (8.72 g) and stirred for 1 hour at room temperature. The mixture was partitioned between hexane/ethyl acetate and water. The organic layer was separated, washed successively with water, sodium sulfite solution, water and brine, dried over magnesium sulfate, and  
25 filtered. The filtrate was concentrated and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to give tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][3-(4-hydroxyphenyl)propyl]carbamate (11.36 g) as a white powder.

30 MS (m/z): 406 (M+H)

Preparation 36

A mixture of methyl 4'-[2-[[[(benzyloxy)carbonyl]-amino]ethyl]-2-methyl-1,1'-biphenyl-4-carboxylate (650 mg),  
35 ammonium formate (500 mg) and palladium on carbon powder

(400 mg) in methanol (10 ml) and water (1.0 ml) was refluxed for 2 hours. The reaction mixture was filtrated and poured into water and extracted with chloroform. The organic layer was washed with brine, dried over magnesium sulfate and  
 5 evaporated to give methyl 4'-(2-aminoethyl)-2-methyl-1,1'-biphenyl-4-carboxylate (380 mg).

(+)ESI-MS (m/z): 270 (M+H)<sup>+</sup>

#### Preparation 37

10 The following compounds were obtained according to a similar manner to that of Preparation 36.

(1) Ethyl 4'-(2-aminoethyl)-2-methoxy-1,1'-biphenyl-4-carboxylate  
 15 MS (m/z): 300 (M+H)

(2) tert-Butyl [2-(4-hydroxyphenyl)ethyl][(2R)-2-hydroxy-2-(3-pyridyl)ethyl]carbamate  
 20 MS (m/z): 359 (M+H)

#### Preparation 38

The following compound was obtained according to a similar manner to that of Example 14.

25 tert-Butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-(4'-formyl-2',3'-dimethyl-1,1'-biphenyl-4-yl)ethyl]carbamate  
 (+)ESI-MS (m/z): 530 (M+Na)<sup>+</sup>

#### Example 14

30 To a solution of tert-butyl [2-(4-bromophenyl)ethyl]-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate (365 mg) in 1,2-dimethoxyethane (6 ml) was added [4-(ethoxycarbonyl)-2-methoxyphenyl]boronic acid (216 mg),  
 tetrakis(triphenylphosphine)palladium (46 mg) and aqueous  
 35 solution of sodium carbonate (2M, 0.85 ml), and the mixture

was stirred at 80°C for 4 hours under nitrogen. The mixture was diluted with ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue  
 5 was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give ethyl 4'-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino]ethyl]-2-methoxy-1,1'-biphenyl-4-carboxylate (222 mg).  
 MS (m/z): 554 (M+H)<sup>+</sup>

10

Example 15

The following compounds were obtained according to a similar manner to that of Example 14.

- 15 (1) 4'-[(2R)-2-[[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]propyl]-3-methoxy-1,1'-biphenyl-4-carboxylic acid hydrochloride  
 NMR (DMSO-d<sub>6</sub>, δ): 1.14 (3H, d, J=6.4Hz), 2.8-3.8 (5H, m), 3.92 (3H, s), 5.0-5.3 (1H, m), 6.3-6.4 (1H, m),  
 20 7.2-7.8 (10H, m), 8.13 (1H, br s), 8.85 (1H, br s), 9.42 (1H, br s)  
 MS (m/z): 440 (M+H)
- (2) 4'-[(2R)-2-[[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]propyl]-2-methoxy-1,1'-biphenyl-4-carboxylic acid  
 25 hydrochloride  
 NMR (DMSO-d<sub>6</sub>, δ): 1.17 (3H, d, J=6.4Hz), 2.8-3.8 (5H, m), 3.83 (3H, s), 5.0-5.2 (1H, m), 6.3-6.4 (1H, m),  
 7.2-7.8 (10H, m), 8.11 (1H, br s), 8.86 (1H, br s),  
 30 9.37 (1H, br s)  
 MS (m/z): 440 (M+H)
- (3) 4'-[(2R)-2-[[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]propyl]-2-methyl-1,1'-biphenyl-4-carboxylic acid  
 35 hydrochloride

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.17 (3H, d,  $J=6.4\text{Hz}$ ), 2.28 (3H, s),  
 2.8-3.8 (5H, m), 5.0-5.3 (1H, m), 6.3-6.4 (1H, m),  
 7.2-7.6 (8H, m), 7.7-7.9 (2H, m), 8.11 (1H, br s),  
 8.86 (1H, br s), 9.39 (1H, br s)

5 MS (m/z): 424 (M+H)

(4) 4'-[(2R)-2-[[ (2S)-2-(3-Chlorophenyl)-2-hydroxyethyl]-  
 amino]propyl]-3-methoxy-1,1'-biphenyl-4-carboxylic acid  
 hydrochloride

10 NMR (DMSO- $d_6$ ,  $\delta$ ): 1.16 (3H, d,  $J=6.4\text{Hz}$ ), 2.8-3.8 (5H,  
 m), 3.91 (3H, s), 5.0-5.3 (1H, m), 6.3-6.4 (1H,  
 m), 7.2-7.8 (11H, m), 8.77 (1H, br s), 9.13 (1H,  
 br s)

MS (m/z): 440 (M+H)

15

(5) 4'-[(2R)-2-[[ (2R)-2-Phenyl-2-hydroxyethyl]amino]-  
 propyl]-3-methoxy-1,1'-biphenyl-4-carboxylic acid  
 hydrochloride

20 NMR (DMSO- $d_6$ ,  $\delta$ ): 1.15 (3H, d,  $J=6.4\text{Hz}$ ), 2.8-3.8 (5H,  
 m), 3.92 (3H, s), 5.0-5.2 (1H, m), 6.3-6.4 (1H, m),  
 7.2-7.6 (9H, m), 7.7-7.9 (3H, m), 8.81 (1H, br s),  
 9.31 (1H, br s)

MS (m/z): 406 (M+H)

25 (6) 4'-[(2R)-2-[[ (2R)-2-Phenyl-2-hydroxyethyl]amino]-  
 propyl]-2-methyl-1,1'-biphenyl-4-carboxylic acid  
 hydrochloride

30 NMR (DMSO- $d_6$ ,  $\delta$ ): 1.17 (3H, d,  $J=6.4\text{Hz}$ ), 2.28 (3H, s),  
 2.8-3.8 (5H, m), 5.0-5.2 (1H, m), 6.3-6.4 (1H, m),  
 7.2-7.6 (9H, m), 7.7-7.9 (3H, m), 8.81 (1H, br s),  
 9.24 (1H, br s)

MS (m/z): 390 (M+H)

35 (7) 4'-[(2R)-2-[[ (2S)-2-Phenyl-2-hydroxyethyl]amino]-  
 propyl]-2-methyl-1,1'-biphenyl-4-carboxylic acid

hydrochloride

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.19 (3H, d,  $J=6.4\text{Hz}$ ), 2.27 (3H, s),  
2.8-3.8 (5H, m), 5.0-5.2 (1H, m), 6.2-6.3 (1H, m),  
7.2-7.6 (9H, m), 7.7-7.9 (3H, m), 8.80 (1H, br s),  
9.35 (1H, br s)

MS (m/z): 390 (M+H)

(8) 4'-[(2R)-2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-  
amino]propyl]-3-isopropoxy-1,1'-biphenyl-4-carboxylic  
acid hydrochloride

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.14 (3H, d,  $J=6.4\text{Hz}$ ), 1.30 (6H, d,  
 $J=5.8\text{Hz}$ ), 2.8-3.8 (5H, m), 4.6-4.9 (1H, m), 5.0-  
5.3 (1H, m), 6.2-6.4 (1H, m), 7.2-7.8 (11H, m),  
8.82 (1H, br s), 9.24 (1H, br s)

MS (m/z): 468 (M+H)

(9) 4'-[(2R)-2-[[ (2R)-2-Phenyl-2-hydroxyethyl]amino]-  
propyl]-3-isopropoxy-1,1'-biphenyl-4-carboxylic acid  
hydrochloride

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.12 (3H, d,  $J=6.4\text{Hz}$ ), 1.30 (6H, d,  
 $J=5.8\text{Hz}$ ), 2.8-3.8 (5H, m), 4.6-4.9 (1H, m), 5.0-  
5.3 (1H, m), 6.2-6.4 (1H, m), 7.2-7.8 (12H, m),  
8.82 (1H, br s)

MS (m/z): 434 (M+H)

(10) 4'-[(2R)-2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-  
amino]propyl]-3-cyclohexyloxy-1,1'-biphenyl-4-  
carboxylic acid hydrochloride

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.14 (3H, d,  $J=6.4\text{Hz}$ ), 1.2-2.0 (10H,  
m), 2.8-3.8 (5H, m), 4.65 (1H, m), 5.0-5.2 (1H, m),  
6.3-6.4 (1H, m), 7.2-7.9 (11H, m), 8.79 (1H, br s),  
9.10 (1H, br s)

MS (m/z): 508 (M+H)

(11) 4'-[(2R)-2-[[ (2R)-2-Phenyl-2-hydroxyethyl]amino]-



propyl]-3-cyclohexyloxy-1,1'-biphenyl-4-carboxylic acid  
hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.14 (3H, d, J=6.4Hz), 1.2-2.0 (10H,  
m), 2.8-3.8 (5H, m), 4.65 (1H, m), 4.9-5.1 (1H, m),  
5 6.23 (1H, m), 7.1-7.9 (12H, m)

MS (m/z): 474 (M+H)

(12) Methyl 4'-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-  
chlorophenyl)-2-hydroxyethyl]amino]ethyl]-3-methoxy-  
10 1,1'-biphenyl-4-carboxylate  
(+)ESI-MS (m/z): 562 (M+Na)<sup>+</sup>

(13) Methyl 4'-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-  
chlorophenyl)-2-hydroxyethyl]amino]ethyl]-2-chloro-  
15 1,1'-biphenyl-4-carboxylate  
(+)ESI-MS (m/z): 544 (M+H)<sup>+</sup>

#### Example 16

To a solution of 4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-  
20 chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl  
trifluoromethanesulfonate (300 mg) in 1,2-dimethoxyethane (5  
ml) was added [3-fluoro-4-(methoxycarbonyl)phenyl]boronic  
acid (125 mg), tetrakis(triphenylphosphine)palladium (53 mg)  
and aqueous solution of sodium carbonate (2M, 0.6 ml), and  
25 the mixture was stirred at 80°C for 2 hours under nitrogen.  
The mixture was diluted with ethyl acetate and water. The  
organic layer was separated, washed with brine, dried over  
magnesium sulfate and evaporated under reduced pressure.  
The residue was purified by column chromatography on silica  
30 gel (hexane/ethyl acetate = 3/1) to give methyl 4'-[2-  
[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]ethyl]-3-fluoro-1,1'-biphenyl-4-  
carboxylate (230 mg).

(+)ESI-MS (m/z): 528 (M+H)<sup>+</sup>

Example 17

The following compound was obtained according to a similar manner to that of Example 16.

5        Methyl 4'-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-3-methyl-1,1'-biphenyl-4-carboxylate

(+)ESI-MS (m/z): 546 (M+Na)<sup>+</sup>

10 Example 18

To a solution of ethyl 4'-[2-[(tert-butoxycarbonyl)-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-2-methoxy-1,1'-biphenyl-4-carboxylate (220 mg) in ethanol (2.0 ml) was added 1N aqueous sodium hydroxide solution (1.2 ml),  
 15 and the mixture was stirred at 40°C for 3 hours. The solvent was removed by evaporation, and the aqueous solution was acidified with 1N hydrochloric acid and extracted with ethyl acetate (30 ml x 2). The combined organic layers were washed with water and brine, dried over magnesium sulfate  
 20 and evaporated under reduced pressure to give a benzoic acid product. To a solution of the product in tetrahydrofuran (1.5 ml) was added 4N hydrochloride in dioxane (1.0 ml), and the mixture was stirred at room temperature for 12 hours. The resultant solid was collected by filtration and dried to  
 25 give 4'-[2-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-ethyl]-2-methoxy-1,1'-biphenyl-4-carboxylic acid hydrochloride (83 mg).

NMR (DMSO-d<sub>6</sub>, δ): 3.02-3.27 (6H, m), 3.82 (3H, s),  
 4.98-5.02 (1H, m), 6.35 (1H, br), 7.30-7.64 (11H,  
 30 m), 9.05 (1H, br)

(-)ESI-MS (m/z): 424 (M-HCl-H)<sup>-</sup>

Example 19

35        The following compounds were obtained according to a similar manner to that of Example 18.

- (1) 4'-[2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-ethyl]-3-methoxy-1,1'-biphenyl-4-carboxylic acid hydrochloride  
5 NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 3.01-3.34 (6H, m), 3.92 (3H, s), 5.02-5.06 (1H, m), 6.37 (1H, br), 7.26-7.48 (9H, m), 7.74 (2H, d, J=7.9Hz), 9.25 (1H, br)  
(-)ESI-MS (m/z): 424 (M-HCl-H)<sup>-</sup>
- 10 (2) 2-Chloro-4'-[2-[[ (2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride  
NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 3.01-3.34 (6H, m), 4.99-5.03 (1H, m), 6.36 (1H, br), 7.37-7.55 (9H, m), 7.93-8.03 (2H, m), 9.10 (1H, br)  
15 (-)ESI-MS (m/z): 424 (M-HCl-H)<sup>-</sup>
- (3) 4'-[2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-ethyl]-3-fluoro-1,1'-biphenyl-4-carboxylic acid hydrochloride  
20 NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 3.01-3.33 (6H, m), 4.98-5.03 (1H, m), 6.34 (1H, br), 7.35-7.47 (6H, m), 7.61-7.98 (5H, m), 9.10 (1H, br)  
(-)ESI-MS (m/z): 412 (M-HCl-H)<sup>-</sup>
- 25 (4) 4'-[2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-ethyl]-3-methyl-1,1'-biphenyl-4-carboxylic acid hydrochloride  
NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 2.60 (3H, s), 3.01-3.34 (6H, m), 4.98-5.02 (1H, m), 6.34 (1H, br), 7.36-7.60 (8H, m), 7.72 (2H, d, J=8.0Hz), 7.91 (1H, d, J=8.0Hz), 9.25 (1H, br)  
30 (-)ESI-MS (m/z): 408 (M-HCl-H)<sup>-</sup>

To a solution of tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-(4'-formyl-2',3'-dimethyl-1,1'-biphenyl-4-yl)ethyl]carbamate in acetonitrile (2.5 ml) and pH 4 buffer solution (sodium dihydrogenphosphate) (1.3 ml) was added 30%  
 5 hydrogen peroxide solution (60  $\mu$ l) and 80% sodium chlorite (128 mg) below 10°C. The reaction mixture was stirred at 40°C for 1.5 hours. The mixture was diluted with ethyl acetate, washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to give a  
 10 benzoic acid product. To a solution of the product in tetrahydrofuran (1.0 ml) was added 4N hydrochloride in dioxane (1.18 ml), and the mixture was stirred at room temperature for 12 hours. The resultant solid was collected by filtration and dried to give 4'-[2-[(2R)-2-(3-  
 15 chlorophenyl)-2-hydroxyethyl]amino]ethyl]-2,3-dimethyl-1,1'-biphenyl-4-carboxylic acid hydrochloride (140 mg).

NMR (DMSO- $d_6$ ,  $\delta$ ): 2.14 (3H, s), 2.45 (3H, s), 3.00-3.34 (6H, m), 4.99-5.03 (1H, m), 6.34 (1H, br), 7.07 (1H, d, J=8.0Hz), 7.05-7.59 (9H, m), 9.25 (1H, br)  
 20 (-)ESI-MS (m/z): 422 (M-HCl-H)<sup>-</sup>

#### Example 21

A solution of ethyl 4'-(3-aminopropyl)-1,1'-biphenyl-4-carboxylate (200 mg), and 2-chloro-5-[(2R)-2-oxiranyl]-  
 25 pyridine (71.5 mg) in ethanol (10 ml) was refluxed for 18 hours. The mixture was evaporated in vacuo. The residue was purified by column chromatography on silica gel (chloroform:methanol = 100:1) to give ethyl 4'-[3-[(2R)-2-(6-chloro-3-pyridyl)-2-hydroxyethyl]amino]propyl]-1,1'-  
 30 biphenyl-4-carboxylate (96 mg) as a colorless foam.

MS (m/z): 439 (M+H)

#### Example 22

The following compounds were obtained according to a  
 35 similar manner to that of Example 21.

(1) Methyl 4'-[2-[[ (2R)-2-(6-chloro-3-pyridyl)-2-hydroxyethyl]amino]ethyl]-2-methyl-1,1'-biphenyl-4-carboxylate

5 (+)ESI-MS (m/z): 425 (M+H)<sup>+</sup>

(2) Ethyl 4'-[2-[[ (2R)-2-(6-chloro-3-pyridyl)-2-hydroxyethyl]amino]ethyl]-2-methoxy-1,1'-biphenyl-4-carboxylate

10 MS (m/z): 454 (M<sup>+</sup>)

### Example 23

To a solution of ethyl 4'-[3-[[ (2R)-2-(6-chloro-3-pyridyl)-2-hydroxyethyl]amino]propyl]-1,1'-biphenyl-4-carboxylate (96 mg) in tetrahydrofuran (3.5 ml) was added  
15 di-tert-butyl dicarbonate (53 mg), and the mixture was stirred at room temperature for 30 minutes and then evaporated. To the residue were added 1N sodium hydroxide solution (0.5 ml) and methanol (0.5 ml), and was stirred for  
20 2 hours at room temperature. The residue was diluted with ethyl acetate and saturated aqueous sodium bicarbonate solution. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel  
25 (hexane/ethyl acetate = 1/1) to give 4'-[3-[(tert-butoxycarbonyl) [(2R)-2-(6-chloro-3-pyridyl)-2-hydroxyethyl]-amino]propyl]-1,1'-biphenyl-4-carboxylic acid (100 mg) as a colorless foam.

MS (m/z): 512 (M+H)

30

### Example 24

The following compounds were obtained according to a similar manner to that of Example 23.

35 (1) 4'-[2-[(tert-Butoxycarbonyl) [(2R)-2-(6-chloro-3-

pyridyl)-2-hydroxyethyl]amino]ethyl]-2-methyl-1,1'-  
biphenyl-4-carboxylic acid  
(+)ESI-MS (m/z): 509 (M-H)<sup>-</sup>

- 5 (2) 4'-[2-[(tert-Butoxycarbonyl)[(2R)-2-(6-chloro-3-  
pyridyl)-2-hydroxyethyl]amino]ethyl]-2-methoxy-1,1'-  
biphenyl-4-carboxylic acid  
MS (m/z): 527 (M+H)

10 Example 25

4'-[3-[(tert-Butoxycarbonyl)[(2R)-2-(6-chloro-3-  
pyridyl)-2-hydroxyethyl]amino]propyl]-1,1'-biphenyl-4-  
carboxylic acid (100 mg), ammonium formate (50 mg) and  
palladium on carbon powder (30 mg) in methanol (5 ml) and  
15 water (1.0 ml) was refluxed for 30 minutes. The reaction  
mixture was filtrated and poured into water and extracted  
with ethyl acetate. The organic layer was washed with brine,  
dried over magnesium sulfate, and evaporated in vacuo. A  
mixture of the residue was chromatographed (chloroform-  
20 methanol) over silica gel to give 4'-[3-[(tert-  
butoxycarbonyl)[(2R)-2-hydroxy-2-(3-pyridyl)ethyl]amino]-  
propyl]-1,1'-biphenyl-4-carboxylic acid (90 mg) as a  
colorless foam.

MS (m/z): 477 (M+H)

25

Example 26

The following compounds were obtained according to a  
similar manner to that of Example 25.

- 30 (1) 4'-[2-[(tert-Butoxycarbonyl)[(2R)-2-hydroxy-2-(3-  
pyridyl)ethyl]amino]ethyl]-2-methyl-1,1'-biphenyl-4-  
carboxylic acid  
(+)ESI-MS (m/z): 475 (M-H)<sup>-</sup>

- 35 (2) 4'-[2-[(tert-Butoxycarbonyl)[(2R)-2-hydroxy-2-(3-

pyridyl)ethyl]amino]ethyl]-2-methoxy-1,1'-biphenyl-4-carboxylic acid

MS (m/z): 493 (M+H)

- 5 (3) 4'-[3-[(tert-Butoxycarbonyl)[(2R)-2-hydroxy-2-(3-pyridyl)ethyl]amino]propyl]-2-methoxy-1,1'-biphenyl-4-carboxylic acid

MS (m/z): 507 (M+H)

- 10 (4) 4'-[(2R)-2-[(tert-Butoxycarbonyl)[(2R)-2-hydroxy-2-(3-pyridyl)ethyl]amino]propyl]-1,1'-biphenyl-4-carboxylic acid

MS (m/z): 477 (M+H)

15 Example 27

A solution of tert-butyl 4'-[3-[(tert-butoxycarbonyl)-[(2R)-2-hydroxy-2-(3-pyridyl)ethyl]amino]propyl]-1,1'-biphenyl-4-carboxylic acid (90 mg) and 4N hydrochloride in dioxane (5.0 ml) was stirred at room temperature for 24 hours. The resultant solid was collected by filtration and dried to give 4'-[3-[[2R)-2-hydroxy-2-(3-pyridyl)ethyl]amino]propyl]-1,1'-biphenyl-4-carboxylic acid dihydrochloride (80 mg) as a white solid.

25 NMR (DMSO-d<sub>6</sub>, δ): 2.90-3.90 (8H, m), 5.10-5.20 (1H, m), 7.35 (1H, d, J=8Hz), 7.65-7.85 (6H, m), 8.05 (1H, d, J=8Hz), 8.25 (1H, d, J=8Hz), 8.70-8.85 (2H, m)

MS (m/z): 377 (M+H)

Example 28

30 The following compounds were obtained according to a similar manner to that of Example 27.

- (1) 4'-[2-[[2R)-2-Hydroxy-2-(3-pyridyl)ethyl]amino]ethyl]-2-methyl-1,1'-biphenyl-4-carboxylic acid  
35 dihydrochloride

NMR (DMSO- $d_6$ ,  $\delta$ ): 3.10-3.80 (6H, m), 3.90 (3H, s),  
 5.10-5.20 (1H, m), 7.40-7.70 (7H, m), 7.8-7.90 (1H,  
 m), 8.25 (1H, d,  $J=8\text{Hz}$ ), 8.70-8.85 (2H, m)  
 (-)ESI-MS ( $m/z$ ): 375 ( $M-2\text{HCl}-\text{H}$ )<sup>-</sup>

5

- (2) 4'-[2-[[ (2R)-2-Hydroxy-2-(3-pyridyl)ethyl]amino]ethyl]-  
 2-methoxy-1,1'-biphenyl-4-carboxylic acid  
 dihydrochloride

10 NMR (DMSO- $d_6$ ,  $\delta$ ): 3.10-3.80 (6H, m), 3.90 (3H, s),  
 5.10-5.20 (1H, m), 7.40-7.70 (7H, m), 7.80-7.90  
 (1H, m), 8.25 (1H, d,  $J=8\text{Hz}$ ), 8.70-8.85 (2H, m)  
 MS ( $m/z$ ): 393 ( $M+\text{H}$ )

- 15 (3) 4'-[3-[[ (2R)-2-Hydroxy-2-(3-pyridyl)ethyl]amino]-  
 propyl]-2-methoxy-1,1'-biphenyl-4-carboxylic acid  
 dihydrochloride

20 NMR (DMSO- $d_6$ ,  $\delta$ ): 2.90-3.90 (8H, m), 3.95 (3H, s),  
 5.10-5.20 (1H, m), 7.35 (1H, d,  $J=8\text{Hz}$ ), 7.65-7.85  
 (6H, m), 8.05 (1H, d,  $J=8\text{Hz}$ ), 8.25 (1H, d,  $J=8\text{Hz}$ ),  
 8.70-8.85 (2H, m)  
 MS ( $m/z$ ): 407 ( $M+\text{H}$ )

- 25 (4) 2-Chloro-4'-[2-[[ (2R)-2-hydroxy-2-(3-pyridyl)ethyl]-  
 amino]ethyl]-1,1'-biphenyl-4-carboxylic acid  
 dihydrochloride

NMR (DMSO- $d_6$ ,  $\delta$ ): 3.10-3.80 (6H, m), 5.10-5.20 (1H, m),  
 7.40-7.70 (7H, m), 7.90-8.10 (2H, m), 8.70-8.85  
 (2H, m)  
 MS ( $m/z$ ): 397 ( $M+\text{H}$ )

30

- (5) 4'-[(2R)-2-[[ (2R)-2-Hydroxy-2-(3-pyridyl)ethyl]amino]-  
 propyl]-1,1'-biphenyl-4-carboxylic acid dihydrochloride

35 NMR (DMSO- $d_6$ ,  $\delta$ ): 1.70 (3H, d,  $J=6\text{Hz}$ ), 3.30-3.90 (6H,  
 m), 5.10-5.20 (1H, m), 7.40-7.70 (7H, m), 7.80-  
 7.90 (1H, m), 8.25 (1H, d,  $J=8\text{Hz}$ ), 8.70-8.85 (2H,



m)

MS (m/z): 377 (M+H)

- 5 (6) 4'-[3-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-  
propyl]-2-methyl-1,1'-biphenyl-4-carboxylic acid  
hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 2.00-2.15 (2H, m), 2.30 (3H, s),  
2.60-3.30 (6H, m), 5.00-5.10 (1H, m), 7.20-7.60  
(9H, m), 7.75-7.90 (2H, m)

10 MS (m/z): 424 (M+H)

Example 29

The following compounds were obtained according to a  
similar manner to that of Example 23.

15

- (1) Ethyl 4'-[3-[(tert-butoxycarbonyl) [(2R)-2-(6-chloro-3-  
pyridyl)-2-hydroxyethyl]amino]propyl]-2-methoxy-1,1'-  
biphenyl-4-carboxylate

MS (m/z): 569 (M+H)

20

- (2) Methyl 4'-[2-[(tert-butoxycarbonyl) [(2R)-2-hydroxy-2-  
(3-pyridyl)ethyl]amino]ethyl]-2-chloro-1,1'-biphenyl-4-  
carboxylate

MS (m/z): 512 (M+H)

25

- (3) Methy 4'-[(2R)-2-[(tert-butoxycarbonyl) [(2R)-2-(6-  
chloro-3-pyridyl)-2-hydroxyethyl]amino]propyl]-1,1'-  
biphenyl-4-carboxylate

MS (m/z): 524 (M+H)

30

- (4) Methyl 4'-[3-[(tert-butoxycarbonyl) [(2R)-2-(3-  
chlorophenyl)-2-hydroxyethyl]amino]propyl]-2-methyl-  
1,1'-biphenyl-4-carboxylate

MS (m/z): 538 (M+H)

35

- (5) 4'-[(2R)-2-[[ (2R)-2-Hydroxy-2-(3-pyridyl)ethyl]amino]-propyl]-3-methoxy-1,1'-biphenyl-4-carboxylic acid dihydrochloride  
 NMR (DMSO-d<sub>6</sub>, δ): 1.14 (3H, d, J=6.4Hz), 2.8-3.8 (5H, m), 3.92 (3H, s), 5.1-5.3 (1H, m), 7.2-7.5 (4H, m), 7.7-7.9 (4H, m), 8.2-8.4 (1H, m), 8.8-9.0 (2H, m), 9.36 (1H, br s)  
 MS (m/z): 407 (M+H)
- 10 (6) 4'-[(2R)-2-[[ (2R)-2-Hydroxy-2-(3-pyridyl)ethyl]amino]-propyl]-2-methoxy-1,1'-biphenyl-4-carboxylic acid dihydrochloride  
 NMR (DMSO-d<sub>6</sub>, δ): 1.14 (3H, d, J=6.4Hz), 2.8-3.8 (5H, m), 3.83 (3H, s), 5.1-5.3 (1H, m), 7.2-7.8 (7H, m), 7.8-8.0 (1H, m), 8.2-8.5 (1H, m), 8.7-9.0 (2H, m), 9.02 (1H, br s), 9.36 (1H, br s)  
 MS (m/z): 407 (M+H)
- 20 (7) 4'-[(2R)-2-[[ (2R)-2-Hydroxy-2-(3-pyridyl)ethyl]amino]-propyl]-2-methyl-1,1'-biphenyl-4-carboxylic acid dihydrochloride  
 NMR (DMSO-d<sub>6</sub>, δ): 1.19 (3H, d, J=6.4Hz), 2.48 (3H, s), 2.8-3.8 (5H, m), 5.1-5.3 (1H, m), 7.2-7.5 (5H, m), 7.8-8.0 (3H, m), 8.37 (1H, d, J=8.2Hz), 8.78 (1H, d, J=4.6Hz), 8.87 (1H, s), 9.04 (1H, br s), 9.35 (1H, br s)  
 MS (m/z): 391 (M+H)
- 30 (8) 4'-[(2R)-2-[[ (2R)-2-Hydroxy-2-(3-pyridyl)ethyl]amino]-propyl]-3-methyl-1,1'-biphenyl-4-carboxylic acid dihydrochloride  
 NMR (DMSO-d<sub>6</sub>, δ): 1.19 (3H, d, J=6.4Hz), 2.60 (3H, s), 2.8-3.8 (5H, m), 5.1-5.3 (1H, m), 7.2-8.0 (8H, m), 8.37 (1H, d, J=8.2Hz), 8.79 (1H, d, J=4.6Hz), 8.87 (1H, s), 9.05 (1H, br s), 9.35 (1H, br s)
- 35

MS (m/z): 391 (M+H)

- 5 (9) 4'-[(2R)-2-[[ (2R)-2-Hydroxy-2-(3-pyridyl)ethyl]amino]-propyl]-3-isopropoxy-1,1'-biphenyl-4-carboxylic acid dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.19 (3H, d, J=6.4Hz), 1.31 (6H, d, J=6.0Hz), 2.8-3.8 (5H, m), 4.6-4.9 (1H, m), 5.1-5.3 (1H, m), 7.2-7.5 (4H, m), 7.6-8.0 (4H, m), 8.37 (1H, d, J=8.2Hz), 8.80 (1H, d, J=4.6Hz), 8.88 (1H, s), 9.02 (1H, br s), 9.35 (1H, br s)

MS (m/z): 435 (M+H)

- 15 (10) 4'-[(2R)-2-[[ (2S)-2-Hydroxy-2-(3-pyridyl)ethyl]amino]-propyl]-1,1'-biphenyl-4-carboxylic acid dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.19 (3H, d, J=6.4Hz), 2.8-3.8 (5H, m), 5.1-5.3 (1H, m), 7.2-8.1 (8H, m), 8.57 (1H, d, J=7.8Hz), 8.81 (1H, d, J=4.6Hz), 8.90 (1H, s), 9.10 (1H, br s), 9.56 (1H, br s)

MS (m/z): 357 (M-H)

20

- (11) 4'-[(2R)-2-[[ (2S)-2-Hydroxy-2-(6-chloro-3-pyridyl)ethyl]amino]propyl]-1,1'-biphenyl-4-carboxylic acid dihydrochloride

25 NMR (DMSO-d<sub>6</sub>, δ): 1.17 (3H, d, J=6.4Hz), 2.8-3.8 (5H, m), 5.1-5.3 (1H, m), 7.39 (2H, d, J=8.0Hz), 7.58 (1H, d, J=8.0Hz), 7.6-8.2 (7H, m), 8.48 (1H, d, J=2.4Hz), 8.86 (1H, br s), 9.22 (1H, br s)

MS (m/z): 409 (M-H)

- 30 (12) 4'-[(2R)-2-[[ (2R)-2-Hydroxy-2-(6-chloro-3-pyridyl)ethyl]amino]propyl]-1,1'-biphenyl-4-carboxylic acid dihydrochloride

35 NMR (DMSO-d<sub>6</sub>, δ): 1.16 (3H, d, J=6.4Hz), 2.8-3.8 (5H, m), 5.1-5.3 (1H, m), 7.38 (2H, d, J=8.0Hz), 7.58 (1H, d, J=8.0Hz), 7.6-8.2 (7H, m), 8.49 (1H, d,

$J=2.4\text{Hz}$ ), 8.86 (1H, br s), 9.45 (1H, br s)

MS (m/z): 409 (M-H)

(13) 4'-[(2R)-2-[[ (2R)-2-Hydroxy-2-(3-pyridyl)ethyl]amino]-propyl]-3-cyclohexyloxy-1,1'-biphenyl-4-carboxylic acid dihydrochloride

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.15 (3H, d,  $J=6.4\text{Hz}$ ), 1.2-2.0 (10H, m), 2.7-3.8 (5H, m), 4.65 (1H, m), 5.31 (1H, m), 7.2-7.5 (5H, m), 7.6-7.8 (2H, m), 7.9-8.0 (1H, m), 8.45 (1H, m), 8.82 (1H, d,  $J=2.6\text{Hz}$ ), 8.90 (1H, s), 9.07 (1H, br s), 9.43 (1H, br s)

MS (m/z): 475 (M+H)

#### Example 30

To a solution of ethyl 4'-[3-[(tert-butoxycarbonyl)-[(2R)-2-(6-chloro-3-pyridyl)-2-hydroxyethyl]amino]propyl]-2-methoxy-1,1'-biphenyl-4-carboxylate in ethanol (5.0 ml) was added 1N sodium hydroxide (1.0 ml) and the mixture was stirred for 2 hours at room temperature. The mixture was diluted with ethyl acetate and 1N hydrochloric acid. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 1/1) to give 4'-[3-[(tert-butoxycarbonyl)[(2R)-2-(6-chloro-3-pyridyl)-2-hydroxyethyl]amino]propyl]-2-methoxy-1,1'-biphenyl-4-carboxylic acid (100 mg).

MS (m/z): 541 (M+H)

#### Example 31

The following compounds were obtained according to a similar manner to that of Example 30.

(1) 4'-[2-[(tert-Butoxycarbonyl)[(2R)-2-hydroxy-2-(3-pyridyl)ethyl]amino]ethyl]-2-chloro-1,1'-biphenyl-4-carboxylic acid

MS (m/z): 497 (M+H)

(2) 4'-[(2R)-2-[(tert-Butoxycarbonyl)[(2R)-2-(6-chloro-3-pyridyl)-2-hydroxyethyl]amino]propyl]-1,1'-biphenyl-4-carboxylic acid

MS (m/z): 511 (M+H)

(3) 4'-[3-[(tert-Butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,1'-biphenyl-4-carboxylic acid

MS (m/z): 524 (M+H)

#### Preparation 39

The following compound was obtained according to a similar manner to that of Preparation 34.

N-[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-3-(3-hydroxyphenyl)propanamide

MS (m/z): 320 (M+H)

#### Preparation 40

The following compound was obtained according to a similar manner to that of Preparation 35.

tert-Butyl N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-N-[3-(3-hydroxyphenyl)propyl]carbamate

MS (m/z): 405 (M+H)

#### Preparation 41

The following compounds were obtained according to a similar manner to that of Preparation 30.

(1) tert-Butyl N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-N-[3-[3-[[[trifluoromethyl]sulfonyl]oxy]phenyl]propyl]-carbamate

MS (m/z): 537 (M+H)

- (2) 4-[2-[N-(tert-Butoxycarbonyl)-N-[(2R)-2-(5-chloro-3-pyridyl)-2-hydroxyethyl]amino]ethyl]phenyl  
5 trifluoromethanesulfonate  
MS (m/z): 525 (M+H)

- (3) Methyl 4-[[[(trifluoromethyl)sulfonyl]oxy]-1-naphthoate  
MS (m/z): 358 (M+Na)

10

- (4) Methyl [4-[[[(trifluoromethyl)sulfonyl]oxy]phenyl]-  
acetate  
NMR (DMSO-d<sub>6</sub>, δ): 3.63(3H, s), 3.90(2H, s), 7.46(4H, s)

- 15 (5) Methyl [3-[[[(trifluoromethyl)sulfonyl]oxy]phenyl]-  
acetate  
NMR (DMSO-d<sub>6</sub>, δ): 3.63(3H, s), 3.83(2H, s), 7.30-  
7.60(4H, m)

- 20 (6) 5-Hydroxy-1-naphthyl trifluoromethanesulfonate  
NMR (DMSO-d<sub>6</sub>, δ): 6.80(2H, d, J=8Hz), 7.20(2H, t,  
J=8Hz), 7.50(2H, d, J=8Hz)

- (7) Ethyl 5-[[[(trifluoromethyl)sulfonyl]oxy]-1-naphthoate  
25

- (8) 4-[2-[N-(tert-Butoxycarbonyl)-N-[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl trifluoromethane-  
sulfonate  
MS (m/z): 490 (M+H)

30

- (9) Methyl 4-(benzyloxy)-2-[[[(trifluoromethyl)sulfonyl]-  
oxy]benzoate  
MS (m/z): 413 (M+Na)

- 35 (10) Methyl 5-[[[(trifluoromethyl)sulfonyl]oxy]-1,1'-

biphenyl-2-carboxylate

MS (m/z): 383 (M+Na)

Preparation 42

5       The following compounds were obtained according to a similar manner to that of Preparation 21.

(1) 4-[2-[[ (2R)-2-(5,6-Dichloro-3-pyridyl)-2-hydroxyethyl]amino]ethyl]phenol

10       MS (m/z): 327 (M+H)

(2) 4-[2-[[ (2R)-2-Hydroxy-2-phenylethyl]amino]ethyl]phenol

MS (m/z): 258 (M+H)

15   Preparation 43

To a solution of 4-[2-[[ (2R)-2-(5,6-dichloro-3-pyridyl)-2-hydroxyethyl]amino]ethyl]phenol (850 mg) in acetic acid (15 ml) and water (1.0 ml) were added tetramethylammonium bromide (5.2 mg) and zinc dust (509 mg),  
20   and the mixture was stirred at 50°C for 10 hours under nitrogen. The mixture was diluted with ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel  
25   (hexane/ethyl acetate = 2/1) to give 4-[2-[[ (2R)-2-(5-chloro-3-pyridyl)-2-hydroxyethyl]amino]ethyl]phenol (500 mg) as a colorless oil.

MS (m/z): 292 (M+H)

30   Preparation 44

The following compounds were obtained according to a similar manner to that of Preparation 26.

(1) tert-Butyl N-[(2R)-2-(5-chloro-3-pyridyl)-2-hydroxyethyl]-N-[2-(4-hydroxyphenyl)ethyl]carbamate  
35

MS (m/z): 393 (M+H)

(2) tert-Butyl N-[(2R)-2-hydroxy-2-phenylethyl]-N-[2-(4-hydroxyphenyl)ethyl]carbamate

5 MS (m/z): 358 (M+H)

#### Preparation 45

To a solution of benzamide (1.42 g) in tetrahydrofuran (50 ml) were added sodium hydride (611 mg) and 4-bromobenzenesulfonyl chloride (3.0 g), and the mixture was stirred at room temperature for 3 hours. The mixture was diluted with ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give N-benzoyl-4-bromobenzenesulfonamide (2.1 g) as a colorless powder.

NMR (CDCl<sub>3</sub>, δ): 7.20-8.10 (8H, m)

#### 20 Preparation 46

The following compounds were obtained according to a similar manner to that of Preparation 12.

(1) 2-Phenoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde

25 MS (m/z): 325 (M+H)

(2) N-Benzoyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide

30 MS (m/z): 386 (M-H)

(3) Methyl 2-isobutyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

35 MS (m/z): 319 (M+H)



- (4) Methyl 2-isopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate  
MS (m/z): 327 (M+Na)
- 5 (5) Methyl 2-propyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate  
MS (m/z): 327 (M+Na)
- 10 (6) Benzyl (1R)-1-methyl-2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethylcarbamate  
MS (m/z): 396 (M+H)

#### Preparation 47

The following compound was obtained according to a  
15 similar manner to that of Example 1.

4-Methoxy-1-naphthoic acid

NMR (DMSO-d<sub>6</sub>, δ): 7.00 (1H, d, J=6Hz), 7.50-7.70 (2H, m),  
8.20-8.30 (2H, m), 9.00 (1H, d, J=8Hz)

20

#### Preparation 48

Under nitrogen, 4-methoxy-1-naphthoic acid (4.33 g) in dichloromethane (45 ml) was added boron tribromide (1M in dichloromethane, 63 ml) dropwise at 0°C, and the mixture was  
25 stirred at the same temperature for 2 hours. The resulting mixture was poured into ice-cold water and the precipitate was collected by filtration. The filter cake was added to the mixture of water and ethyl acetate, and then adjusted to pH 9 with 1N sodium hydroxide. After separation, the  
30 organic layer was dried over anhydrous magnesium sulfate and evaporated in vacuo to afford 4-hydroxy-1-naphthoic acid (2.19 g) as a colorless powder.

MS (m/z): 187 (M-H)

#### 35 Preparation 49

To a solution of 4-hydroxy-1-naphthoic acid (2.18 g) in methanol (15 ml) was added sulfuric acid (1.0 ml), and the mixture was stirred at 70°C for 3 hours. The solution was diluted with water and ethyl acetate. The organic layer was separated and washed with brine. The extract was dried over magnesium sulfate, filtrated and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with ethyl acetate and hexane to give methyl 4-hydroxy-1-naphthoate (1.64 g) as a white solid.

MS (m/z): 239 (M+Na)

#### Preparation 50

The following compounds were obtained according to a similar manner to that of Preparation 16.

15

(1) Methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthoate

MS (m/z): 313 (M+H)

20

(2) Methyl [4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]acetate

NMR (DMSO-d<sub>6</sub>, δ): 1.66(12H, s), 3.60(3H, s), 3.70(2H, s), 7.20(2H, d, J=8Hz), 7.60(2H, d, J=8Hz)

25

(3) Methyl [3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]acetate

NMR (DMSO-d<sub>6</sub>, δ): 3.60(3H, s), 3.82(2H, s), 7.20-7.60(6H, m)

30

(4) Methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,1'-biphenyl-2-carboxylate

MS (m/z): 361 (M+Na)

#### Preparation 51

35

To a solution of 4-bromo-2-fluorobenzaldehyde (5.0 g)

in dimethylsulfoxide (40 ml) were added phenol (2.78 g) and potassium carbonate (4.08 g), and the mixture was stirred at 100°C for 3 hours. The solution was diluted with water and ethyl acetate. The organic layer was separated and washed  
 5 with brine. The extract was dried over magnesium sulfate, filtrated and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with ethyl acetate and hexane to give 4-bromo-2-phenoxy-1-benzaldehyde (7.3 g) as a white solid.

10 NMR (CDCl<sub>3</sub>,  $\delta$ ): 6.90-7.60 (7H, m), 7.80 (1H, d, J=8Hz),  
 10.48 (1H, s)

#### Preparation 52

The following compounds were obtained according to a  
 15 similar manner to that of Preparation 14.

(1) 4-(2-Methoxy-2-oxoethyl)phenylboronic acid  
 MS (m/z): 193 (M-H)

20 (2) 3-(2-Methoxy-2-oxoethyl)phenylboronic acid  
 MS (m/z): 194 (M+H)

(3) 4-[(2R)-2-[(benzyloxy)carbonyl]amino]propyl]-  
 phenylboronic acid  
 25 MS (m/z): 312 (M-H)

(4) 4-[2-[N-Benzyl-N-(tert-butoxycarbonyl)amino]ethyl]-  
 phenylboronic acid  
 (-)ESI-MS m/z: 354 (M-H)<sup>-</sup>

30

#### Preparation 53

The following compounds were obtained according to a similar manner to that of Preparation 23.

35 (1) Methyl [4'-[(2R)-2-[(benzyloxy)carbonyl]amino]propyl]-

1,1'-biphenyl-4-yl]acetate.

MS (m/z): 418 (M+H)

(2) Ethyl 5-[4-[(2R)-2-[(benzyloxy)carbonyl]amino]propyl]-phenyl]-1-naphthoate

MS (m/z): 490 (M+Na)

(3) Methyl 5-(benzyloxy)-1,1'-biphenyl-2-carboxylate

MS (m/z): 341 (M+Na)

#### Preparation 54

The following compounds were obtained according to a similar manner to that of Preparation 36.

(1) Methyl [4'-[(2R)-2-aminopropyl]-1,1'-biphenyl-4-yl]acetate

MS (m/z): 284 (M+H)

(2) Ethyl 5-[4-[(2R)-2-aminopropyl]phenyl]-1-naphthoate

MS (m/z): 356 (M+Na)

(3) Methyl 5-hydroxy-1,1'-biphenyl-2-carboxylate

MS (m/z): 251 (M+Na)

#### Preparation 55

To a mixture of 5-hydroxy-1-naphthyl trifluoromethanesulfonate (8.0 g) in N,N-dimethylformamide (35 ml) and ethanol (5.0 ml) were added 1,3-bis(diphenylphosphino)propane (621 mg), palladium acetate(II) (3.7 mg) and triethylamine (1.35 g), and the mixture was stirred at 100°C for 1 hour under carbon-monoxide. The mixture was diluted with ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 5/1) to

give ethyl 5-hydroxy-1-naphthoate (1.7 g) as a colorless oil.

MS (m/z): 239 (M+Na)

#### Preparation 56

5 To a solution of 4-bromo-2-fluorobenzoic acid (2.0 g)  
in tetrahydrofuran (15 ml) was added 2M isobutylmagnesium  
bromide in diethyl ether (13.5 ml) dropwise on ice-cooling,  
and the mixture was stirred at 0°C for 1 hour. The mixture  
was diluted with ethyl acetate and water. The organic layer  
10 was separated, washed with brine, dried over magnesium  
sulfate and evaporated. To the solution of the residue in  
N,N-dimethylformamide (20 ml) was added methyl iodide (1.14  
g) and potassium carbonate (1.89 g), and the mixture was  
stirred at 20°C for 3 hours. The mixture was diluted with  
15 ethyl acetate and water. The organic layer was separated,  
washed with brine, dried over magnesium sulfate and  
evaporated. The residue was purified by column  
chromatography on silica gel (hexane/ethyl acetate = 2/1) to  
give methyl 4-bromo-2-isobutylbenzoate (1.5 g) as a  
20 colorless oil.

NMR (DMSO-d<sub>6</sub>, δ): 0.80 (6H, d, J=8Hz), 1.80-2.00 (1H, m),  
2.80 (2H, d, J=8Hz), 3.80 (3H, s), 7.40-7.80 (3H, m)

#### Preparation 57

25 The following compounds were obtained according to a  
similar manner to that of Preparation 56.

(1) Methyl 4-bromo-2-isopropylbenzoate

NMR (DMSO-d<sub>6</sub>, δ): 1.20 (6H, d, J=7Hz), 3.50-3.60 (1H, m),  
30 3.83 (1H, s), 7.50-7.70 (3H, m)  
MS (m/z): 516 (M+H)

(2) Methyl 4-bromo-2-propylbenzoate

NMR (DMSO-d<sub>6</sub>, δ): 0.85 (3H, t, J=7Hz), 1.40-1.70 (2H, m),  
35 2.80-3.00 (2H, m), 3.82 (3H, s), 7.60-7.70 (3H, m)

Preparation 58

The following compound was obtained according to a similar manner to that of Preparation 28.

5

tert-Butyl N-((2R)-2-hydroxy-2-phenylethyl)-N-[(1R)-2-(4-iodophenyl)-1-methylethyl]carbamate

MS (m/z): 482 (M+H)

10 Preparation 59

The following compounds were obtained according to a similar manner to that of Preparation 13.

(1) tert-Butyl N-benzyl-N-[2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethyl]carbamate  
 15 (+)ESI-MS m/z: 460 (M+Na)<sup>+</sup>

(2) 2-(1-Piperidinyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde  
 20 (+)ESI-MS m/z: 581 (M+Na)<sup>+</sup>

Preparation 60

To a solution of 2-(3-methoxyphenyl)ethanamine (5.6 g) in dichloromethane (50 ml) was added 1M boron tribromide in  
 25 dichloromethane (75 ml). The mixture was stirred at 20°C for 16 hours and evaporated in vacuo. To the residue, saturated sodium bicarbonate (50 ml) and tetrahydrofuran (150 ml) were added. The pH value of the mixture was kept between 7 to 8 with 1N aqueous sodium hydroxide solution.  
 30 To the mixture, a solution of di-tert-butyl dicarbonate (8.08 g) in tetrahydrofuran (10 ml) was added, stirred at 20°C for 1 hour. The mixture was diluted with ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated to give  
 35 tert-butyl 2-(3-hydroxyphenyl)ethylcarbamate (8.2 g).

(+)ESI-MS m/z: 260 (M+Na)<sup>+</sup>

#### Preparation 61

To a solution of tert-butyl 2-(3-hydroxyphenyl)-  
5 ethylcarbamate (730 mg) and potassium carbonate (893 mg) in  
N,N-dimethylformamide (10 ml) was added methyl 4-bromo-(3-  
bromomethyl)benzoate (1.52 g), and the mixture was stirred  
at room temperature for 16 hours. The mixture was  
partitioned between ethyl acetate and water. The organic  
10 layer was separated, washed with water and brine, dried over  
magnesium sulfate and evaporated under reduced pressure.  
The residue was purified by column chromatography on silica  
gel (hexane/ethyl acetate = 2/1) to give methyl 4-bromo-3-  
[[3-[2-[(tert-butoxycarbonyl)amino]ethyl]phenoxy]methyl]-  
15 benzoate (970 mg).

(+)ESI-MS m/z: 464 (M+H)<sup>+</sup>

#### Preparation 62

To a solution of methyl 4-bromo-3-[[3-[2-[(tert-  
20 butoxycarbonyl)amino]ethyl]phenoxy]methyl]benzoate (410 mg)  
in N,N-dimethylacetamide (4.0 ml) was added  
dichlorobis(triphenylphosphine)palladium(II) (124 mg) and  
sodium acetate (362 mg), and the mixture was stirred at  
130°C for 1.5 hours under nitrogen. The mixture was cooled  
25 to room temperature, diluted with ethyl acetate and water.  
The organic layer was separated, washed with brine, dried  
over magnesium sulfate and evaporated. The residue was  
purified by column chromatography on silica gel  
(hexane/ethyl acetate = 3/1) to give methyl 3-[2-[(tert-  
30 butoxycarbonyl)amino]ethyl]-6H-benzo[c]chromene-8-  
carboxylate (190 mg).

(+)ESI-MS m/z: 406 (M+Na)<sup>+</sup>

#### Preparation 63

35 The following compounds were obtained according to a

similar manner to that of Example 7.

- (1) Ethyl 6-[4-[2-[N-benzyl-N-(tert-butoxycarbonyl)amino]-ethyl]phenyl]nicotinate

5 (+)ESI-MS m/z: 461 (M+H)<sup>+</sup>

- (2) Methyl 4'-[2-[N-benzyl-N-(tert-butoxycarbonyl)amino]-ethyl]-2,6-dimethyl-1,1'-biphenyl-4-carboxylate

10 (+)ESI-MS m/z: 474 (M+H)<sup>+</sup>

#### Preparation 64

The following compounds were obtained according to a similar manner to that of Example 27.

- 15 (1) Methyl 3-(2-aminoethyl)-6H-benzo[c]chromene-8-carboxylate

(+)ESI-MS m/z: 284 (M+H)<sup>+</sup>

- 20 (2) Ethyl 6-[4-[2-(benzylamino)ethyl]phenyl]nicotinate hydrochloride

(+)ESI-MS m/z: 361 (M+H)<sup>+</sup>

#### Preparation 65

25 The following compounds were obtained according to a similar manner to that of Preparation 16.

- (1) 3-[2-[N-(tert-Butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl trifluoromethanesulfonate

30 (+)ESI-MS m/z: 546 (M+Na)<sup>+</sup>

- (2) 4-[2-[N-(tert-Butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-2-methoxyphenyl trifluoromethanesulfonate

35 (+)ESI-MS m/z: 576 (M+Na)<sup>+</sup>



(3) 4-[2-[N-(tert-Butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-2-chlorophenyl trifluoromethanesulfonate

5 (+)ESI-MS m/z: 581 (M+Na)<sup>+</sup>

#### Preparation 66

The following compound was obtained according to a similar manner to that of Example 5.

10

Methyl 4'-[2-(benzylamino)ethyl]-2,6-dimethyl-1,1'-biphenyl-4-carboxylate

(+)ESI-MS m/z: 374 (M+H)<sup>+</sup>

#### 15 Preparation 67

To a mixture of 3-chloro-4-hydroxyphenylacetic acid (2.96 g), (1R)-2-amino-1-(3-chlorophenyl)ethanol hydrochloride (3.0 g), and 1-hydroxybenzotriazole (2.14 g) in N,N-dimethylformamide (20 ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (2.46 g), and the mixture was stirred at room temperature for 2 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed successively with sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure to give an amide product. To a tetrahydrofuran (30 ml) solution of the product, 2M borane-dimethyl sulfide complex in tetrahydrofuran (23 ml) was added at room temperature, and the mixture was refluxed for 30 minutes. To the mixture, 6N hydrochloride acid (29.5 ml) was added dropwise below 10°C, and the mixture was stirred at room temperature for 3 hours. To the reaction mixture, 3N aqueous sodium hydroxide solution (58 ml) below 10°C was added and di-tert-butyl dicarbonate (3.46 g) was added portionally at room temperature. The pH value was kept between 7 to 8 by using

20

25

30

35

1N aqueous sodium hydroxide solution. The mixture was stirred at room temperature for 1 hour. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give tert-butyl N-[2-(3-chloro-4-hydroxyphenyl)ethyl]-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate (7.0 g).

(+)ESI-MS m/z: 448 (M+Na)<sup>+</sup>

#### Preparation 68

The following compound was obtained according to a similar manner to that of Preparation 67.

tert-Butyl N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-N-[2-(4-hydroxy-3-methoxyphenyl)ethyl]carbamate  
(+)ESI-MS m/z: 444 (M+Na)<sup>+</sup>

#### Preparation 69

A mixture of 4-bromo-2-fluorobenzaldehyde (3.0 g), piperidine (2.93 ml) and potassium carbonate (5.11 g) in N,N-dimethylformamide (30 ml) was stirred at 100°C for 12 hours. The mixture was cooled to room temperature. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water, saturated aqueous ammonium chloride solution and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 9/1) to give 4-bromo-2-(1-piperidinyl)benzaldehyde (3.5 g).

(+)ESI-MS m/z: 268 (M+H)<sup>+</sup>

#### Preparation 70

The following compound was obtained according to a

similar manner to that of Example 23.

tert-Butyl N-benzyl-N-[2-(4-bromophenyl)ethyl]carbamate  
(+)ESI-MS m/z: 390 (M+H)<sup>+</sup>

5

### Example 32

The following compounds were obtained according to a similar manner to that of Example 7.

- 10 (1) 4'-[(2R)-2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]propyl]-3-propoxy-1,1'-biphenyl-4-carboxylic acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.05(3H, t, J=7.4Hz), 1.35(3H, d, J=6.2Hz), 1.6-1.9(2H, m), 2.8-3.8(5H, m), 4.11(2H, t, J=7.4Hz), 5.0-5.3(1H, m), 6.3-6.4(1H, m), 7.2-7.8(11H, m), 8.55(1H, br s), 9.19(1H, br s)

15

MS m/z: 468 (M+H)

- 20 (2) 4'-[2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-ethyl]-3-hydroxy-1,1'-biphenyl-4-carboxylic acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 2.8-3.0(6H, m), 4.8-5.0(1H, m), 6.33(1H, m), 7.0-7.9(11H, m)

MS m/z: 411 (M+H)

25

- (3) 3-Hydroxy-4'-[(2R)-2-[[ (2R)-2-hydroxy-2-phenylethyl]-amino]propyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.12(3H, d, J=6.4Hz), 2.6-3.2(5H, m), 4.9-5.1(1H, m), 6.23(1H, m), 7.2-7.9(11H, m), 8.77(1H, br s), 9.03(1H, br s)

30

MS m/z: 392 (M+H)

- 35 (4) 3-Ethoxy-4'-[(2R)-2-[[ (2R)-2-hydroxy-2-phenylethyl]-amino]propyl]-1,1'-biphenyl-4-carboxylic acid

hydrochloride

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.15 (3H, d,  $J=6.4$ Hz), 1.36 (3H, t,  $J=7.0$ Hz), 2.6-3.2 (5H, m), 4.21 (2H, q,  $J=7.0$ Hz), 4.9-5.1 (1H, m), 6.23 (1H, m), 7.2-7.7 (11H, m)

5 MS m/z: 418 (M-H)

(5) 4'-[(2R)-2-[[ (2R)-2-Hydroxy-2-phenylethyl]amino]-propyl]-3-propoxy-1,1'-biphenyl-4-carboxylic acid hydrochloride

10 NMR (DMSO- $d_6$ ,  $\delta$ ): 1.03 (3H, t,  $J=7.4$ Hz), 1.12 (3H, d,  $J=6.4$ Hz), 1.74 (2H, m), 2.6-3.2 (5H, m), 4.11 (2H, q,  $J=7.0$ Hz), 4.9-5.1 (1H, m), 6.23 (1H, m), 7.2-7.7 (11H, m)

MS m/z: 434 (M+H)

15

(6) 3-Butoxy-4'-[(2R)-2-[[ (2R)-2-hydroxy-2-phenylethyl]-amino]propyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride

20 NMR (DMSO- $d_6$ ,  $\delta$ ): 0.94 (3H, t,  $J=7.4$ Hz), 1.12 (3H, d,  $J=6.4$ Hz), 1.3-1.8 (4H, m), 2.6-3.2 (5H, m), 4.15 (2H, q,  $J=7.0$ Hz), 4.9-5.1 (1H, m), 6.23 (1H, m), 7.2-7.7 (11H, m)

MS m/z: 448 (M+H)

25 (7) 4'-[(2R)-2-[[ (2R)-2-Hydroxy-2-phenylethyl]amino]-propyl]-3-(pentyloxy)-1,1'-biphenyl-4-carboxylic acid hydrochloride

30 NMR (DMSO- $d_6$ ,  $\delta$ ): 0.89 (3H, t,  $J=7.4$ Hz), 1.13 (3H, d,  $J=6.4$ Hz), 1.2-1.8 (6H, m), 2.6-3.2 (5H, m), 4.14 (2H, q,  $J=7.0$ Hz), 4.9-5.1 (1H, m), 6.23 (1H, m), 7.2-7.7 (11H, m)

MS m/z: 462 (M+H)

35 (8) 3-(Heptyloxy)-4'-[(2R)-2-[[ (2R)-2-hydroxy-2-phenylethyl]amino]propyl]-1,1'-biphenyl-4-carboxylic

acid hydrochloride

NMR (DMSO- $d_6$ ,  $\delta$ ): 0.86(3H, t,  $J=7.4\text{Hz}$ ), 1.16(3H, d,  $J=6.4\text{Hz}$ ), 1.1-1.8(10H, m), 2.6-3.2(5H, m), 4.14(2H, q,  $J=7.0\text{Hz}$ ), 4.9-5.1(1H, m), 6.23(1H, m), 7.2-7.7(11H, m)

MS  $m/z$ : 490 (M+H)

(9) 4'-[(2R)-2-[[ (2R)-2-Hydroxy-2-phenylethyl]amino]-propyl]-3-isobutoxy-1,1'-biphenyl-4-carboxylic acid hydrochloride

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.03(6H, t,  $J=6.2\text{Hz}$ ), 1.16(3H, d,  $J=6.4\text{Hz}$ ), 1.8-2.2(1H, m), 2.6-3.2(5H, m), 3.93(2H, d,  $J=6.2\text{Hz}$ ), 4.9-5.1(1H, m), 6.23(1H, m), 7.2-7.7(11H, m)

MS  $m/z$ : 448 (M+H)

(10) 3-(Allyloxy)-4'-[(2R)-2-[[ (2R)-2-hydroxy-2-phenylethyl]amino]propyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.16(3H, d,  $J=6.4\text{Hz}$ ), 2.6-3.2(5H, m), 4.77(2H, m), 4.9-5.1(1H, m), 5.27(1H, dd,  $J=1.8, 10.6\text{Hz}$ ), 5.40(1H, dd,  $J=1.8, 17.2\text{Hz}$ ), 5.9-6.2(1H, m), 6.23(1H, m), 7.2-7.7(11H, m)

MS  $m/z$ : 432 (M+H)

25

(11) 4'-[(2R)-2-[[ (2R)-2-Hydroxy-2-phenylethyl]amino]-propyl]-3-[(2-methyl-2-propenyl)oxy]-1,1'-biphenyl-4-carboxylic acid hydrochloride

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.16(3H, d,  $J=6.4\text{Hz}$ ), 1.69(3H, s), 2.6-3.2(5H, m), 4.77(2H, m), 4.65(2H, s), 4.9-5.1(1H, m), 4.9-5.2(2H, m), 6.23(1H, m), 7.2-7.7(11H, m)

MS  $m/z$ : 446 (M+H)

35

(12) 3-(2-Fluoroethoxy)-4'-[(2R)-2-[[ (2R)-2-hydroxy-2-

phenylethyl]amino]propyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.16(3H, d, J=6.4Hz), 2.6-3.2(5H, m), 4.3-4.8(4H, m), 4.9-5.1(1H, m), 6.23(1H, m), 7.2-7.7(11H, m)

MS m/z: 438 (M+H)

(13) 3-(2,2-Difluoroethoxy)-4'-[(2R)-2-[(2R)-2-hydroxy-2-phenylethyl]amino]propyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.13(3H, d, J=6.4Hz), 2.6-3.2(5H, m), 4.3-4.7(2H, m), 4.9-5.1(1H, m), 6.0-6.5(2H, m), 7.2-7.7(11H, m)

MS m/z: 456 (M+H)

15

(14) 4'-[(2R)-2-[(2R)-2-Hydroxy-2-phenylethyl]amino]-propyl]-3-(2,2,2-trifluoroethoxy)-1,1'-biphenyl-4-carboxylic acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.13(3H, d, J=6.4Hz), 2.6-3.2(5H, m), 4.7-5.1(3H, m), 6.24(1H, m), 7.2-7.7(11H, m)

MS m/z: 472 (M-H)

20

(15) 3-(2-Hydroxyethoxy)-4'-[(2R)-2-[(2R)-2-hydroxy-2-phenylethyl]amino]propyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.13(3H, d, J=6.4Hz), 2.6-3.2(5H, m), 3.8(2H, m), 4.15(2H, m), 4.9-5.1(1H, m), 6.24(1H, m), 7.2-7.7(11H, m)

MS m/z: 434 (M-H)

30

(16) 4'-[(2R)-2-[(2R)-2-Hydroxy-2-phenylethyl]amino]-propyl]-3-(2-methoxyethoxy)-1,1'-biphenyl-4-carboxylic acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.12(3H, d, J=6.4Hz), 2.6-3.2(5H, m), 3.33(3H, s), 3.70(2H, m), 4.29(2H, m), 4.9-5.1(1H,

35

m), 6.22(1H, m), 7.2-7.7(11H, m)

MS m/z: 450 (M+H)

(17) 3-(3-Fluoropropoxy)-4'-[(2R)-2-[(2R)-2-hydroxy-2-phenylethyl]amino]propyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.13(3H, d, J=6.4Hz), 2.0-2.4(2H, m), 2.6-3.2(5H, m), 4.25(2H, t, J=6.0Hz), 4.56(1H, t, J=5.8Hz), 4.83(1H, t, J=6.0Hz), 4.9-5.1(1H, m), 6.24(1H, m), 7.2-7.7(11H, m)

MS m/z: 452 (M+H)

(18) 4'-[(2R)-2-[(2R)-2-Hydroxy-2-phenylethyl]amino]-propyl]-3-(3,3,3-trifluoropropoxy)-1,1'-biphenyl-4-carboxylic acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.13(3H, d, J=6.4Hz), 2.6-3.2(7H, m), 4.39(2H, t, J=6.0Hz), 4.9-5.1(1H, m), 6.24(1H, m), 7.2-7.7(11H, m)

MS m/z: 488 (M+H)

(19) 3-(Cyclopropyloxy)-4'-[(2R)-2-[(2R)-2-hydroxy-2-phenylethyl]amino]propyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.13(3H, d, J=6.4Hz), 2.6-3.2(5H, m), 4.9-5.1(2H, m), 6.24(1H, m), 7.2-7.7(11H, m)

MS m/z: 432 (M+H)

(20) 3-(Cyclobutyloxy)-4'-[(2R)-2-[(2R)-2-hydroxy-2-phenylethyl]amino]propyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.13(3H, d, J=6.4Hz), 1.2-2.4(6H, m), 2.6-3.2(5H, m), 4.9-5.1(2H, m), 6.24(1H, m), 7.2-7.7(11H, m)

MS m/z: 446 (M+H)

- (21) 3-(Cyclopentyloxy)-4'-[(2R)-2-[(2R)-2-hydroxy-2-phenylethyl]amino]propyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.13(3H, d, J=6.4Hz), 1.2-2.0(8H, m),  
5 2.6-3.2(5H, m), 4.9-5.1(2H, m), 6.24(1H, m), 7.2-7.7(11H, m)  
MS m/z: 460 (M+H)
- (22) 3-(Cyclopropylmethoxy)-4'-[(2R)-2-[(2R)-2-hydroxy-2-phenylethyl]amino]propyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride  
10 NMR (DMSO-d<sub>6</sub>, δ): 0.2-0.7(2H, m), 0.9-1.3(6H, m), 2.6-3.2(5H, m), 4.03(2H, d, J=6.6Hz), 4.9-5.1(1H, m), 6.24(1H, m), 7.2-7.7(11H, m)  
15 MS m/z: 446 (M+H)
- (23) 3-(Cyclohexylmethoxy)-4'-[(2R)-2-[(2R)-2-hydroxy-2-phenylethyl]amino]propyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride  
20 NMR (DMSO-d<sub>6</sub>, δ): 1.0-1.9(14H, m), 2.6-3.2(5H, m), 3.93(2H, d, J=6.6Hz), 4.9-5.1(1H, m), 6.24(1H, m), 7.2-7.7(11H, m)  
MS m/z: 488 (M+H)
- (24) 4'-[2-[(2R)-2-Phenyl-2-hydroxyethyl]amino]ethyl]-1,1'-biphenyl-4-nitrile  
25 MS m/z: 457 (M+H)
- (25) 4'-[(2R)-2-[(2R)-2-Hydroxy-2-phenylethyl]amino]propyl]-3-phenoxy-1,1'-biphenyl-4-carboxylic acid hydrochloride  
30 NMR (DMSO-d<sub>6</sub>, δ): 1.13(3H, d, J=6.4Hz), 2.6-3.2(5H, m), 4.9-5.1(1H, m), 6.24(1H, m), 6.8-7.9(16H, m)  
35 MS m/z: 468 (M+H)



- (26) 4'-[2-[[ (2R)-2-Hydroxy-2-phenylethyl]amino]ethyl]-3-methoxy-1,1'-biphenyl-4-carboxylic acid hydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 2.8-3.3 (6H, m), 4.9-5.1 (1H, m),  
6.22 (1H, m), 7.2-7.8 (12H, m)  
5 MS m/z: 392 (M+H)
- (27) 3-Ethoxy-4'-[2-[[ (2R)-2-hydroxy-2-phenylethyl]amino]-ethyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.35 (3H, t, J=6.8Hz), 2.8-3.3 (6H, m),  
10 4.20 (2H, q, J=6.8Hz), 4.9-5.1 (1H, m), 6.22 (1H, m),  
7.2-7.8 (12H, m)  
MS m/z: 406 (M+H)
- (28) 4'-[2-[[ (2R)-2-Hydroxy-2-phenylethyl]amino]ethyl]-3-propoxy-1,1'-biphenyl-4-carboxylic acid hydrochloride  
15 NMR (DMSO-d<sub>6</sub>, δ): 1.01 (3H, t, J=6.8Hz), 1.6-1.9 (2H, m),  
2.9-3.4 (6H, m), 4.11 (2H, q, J=6.8Hz), 4.9-5.1 (1H, m),  
6.22 (1H, m), 7.2-7.8 (12H, m)  
MS m/z: 420 (M+H)  
20
- (29) 4'-[2-[[ (2R)-2-Hydroxy-2-phenylethyl]amino]ethyl]-3-isopropoxy-1,1'-biphenyl-4-carboxylic acid hydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.31 (6H, t, J=6.8Hz), 2.9-3.4 (6H, m),  
25 4.7-4.9 (1H, m), 4.9-5.1 (1H, m), 6.22 (1H, m), 7.2-7.8 (12H, m)  
MS m/z: 420 (M+H)
- (30) 4'-[2-[[ (2R)-2-Hydroxy-2-phenylethyl]amino]ethyl]-3-isobutoxy-1,1'-biphenyl-4-carboxylic acid hydrochloride  
30 NMR (DMSO-d<sub>6</sub>, δ): 1.02 (6H, t, J=6.8Hz), 1.9-2.1 (1H, m),  
2.9-3.4 (6H, m), 3.92 (2H, d, J=6.8Hz), 4.9-5.1 (1H, m),  
6.22 (1H, m), 7.2-7.8 (12H, m)  
MS m/z: 434 (M+H)  
35

(31) 3-(Allyloxy)-4'-[2-[[ (2R)-2-hydroxy-2-phenylethyl]-amino]ethyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride

5 NMR (DMSO-d<sub>6</sub>, δ): 2.9-3.4 (6H, m), 3.92 (2H, d, J=6.8Hz),  
4.72 (2H, m), 5.2-5.7 (2H, m), 4.9-5.1 (1H, m), 6.0-  
6.2 (1H, m), 6.22 (1H, m), 7.2-7.8 (12H, m)

MS m/z: 418 (M+H)

10 (32) 3-(2-Fluoroethoxy)-4'-[2-[[ (2R)-2-hydroxy-2-phenylethyl]amino]ethyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 2.9-3.4 (6H, m), 4.3-4.7 (3H, m), 4.8-  
4.9 (1H, m), 4.9-5.1 (1H, m), 6.22 (1H, m), 7.2-  
7.8 (12H, m)

15 MS m/z: 424 (M+H)

(33) 3-(3-Fluoropropoxy)-4'-[2-[[ (2R)-2-hydroxy-2-phenylethyl]amino]ethyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride

20 NMR (DMSO-d<sub>6</sub>, δ): 1.9-2.3 (2H, m), 2.9-3.4 (6H, m),  
4.25 (2H, t, J=6.0Hz), 4.56 (1H, t, J=5.9Hz),  
4.80 (1H, t, J=5.8Hz), 4.9-5.1 (1H, m), 6.22 (1H, m),  
7.2-7.8 (12H, m)

MS m/z: 438 (M+H)

25

(34) 3-(Cyclopropyloxy)-4'-[2-[[ (2R)-2-hydroxy-2-phenylethyl]amino]ethyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride

30 NMR (DMSO-d<sub>6</sub>, δ): 2.9-3.4 (6H, m), 4.9-5.1 (1H, m),  
6.22 (1H, m), 7.2-7.8 (12H, m)

MS m/z: 392 (M+H)

35 (35) 3-(Cyclohexyloxy)-4'-[2-[[ (2R)-2-hydroxy-2-phenylethyl]amino]ethyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.2-2.0 (10H, m), 2.9-3.4 (6H, m),  
4.64 (1H, m), 4.9-5.1 (1H, m), 6.22 (1H, m), 7.2-  
7.8 (12H, m)

MS m/z: 460 (M+H)

5

(36) 4'-[2-[[ (2R)-2-Hydroxy-2-phenylethyl]amino]ethyl]-3-  
phenoxy-1,1'-biphenyl-4-carboxylic acid hydrochloride

NMR (DMSO- $d_6$ ,  $\delta$ ): 2.9-3.4 (6H, m), 4.9-5.1 (1H, m),  
6.22 (1H, m), 6.9-8.0 (17H, m)

10

MS m/z: 454 (M+H)

(37) 3-(Benzyloxy)-4'-[2-[[ (2R)-2-hydroxy-2-  
phenylethyl]amino]ethyl]-1,1'-biphenyl-4-carboxylic  
acid hydrochloride

15

NMR (DMSO- $d_6$ ,  $\delta$ ): 2.9-3.4 (6H, m), 4.9-5.1 (1H, m),  
5.33 (2H, m), 6.22 (1H, m), 7.2-7.8 (17H, m)

MS m/z: 468 (M+H)

20

(38) 4'-[2-[[ (2R)-2-Hydroxy-2-phenylethyl]amino]ethyl]-3-  
(2,2,2-trifluoroethoxy)-1,1'-biphenyl-4-carboxylic acid  
hydrochloride

NMR (DMSO- $d_6$ ,  $\delta$ ): 2.9-3.4 (6H, m), 4.3-5.1 (2H, m),  
6.22 (1H, m), 7.2-7.8 (12H, m)

MS m/z: 460 (M+H)

25

(39) 4'-[2-[[ (2R)-2-Hydroxy-2-phenylethyl]amino]ethyl]-2-  
methyl-1,1'-biphenyl-4-carboxylic acid hydrochloride

NMR (DMSO- $d_6$ ,  $\delta$ ): 2.28 (3H, s), 2.9-3.4 (6H, m), 4.9-  
5.1 (1H, m), 5.33 (2H, m), 6.22 (1H, m), 7.2-7.8 (12H,  
m)

30

MS m/z: 476 (M+H)

35

(40) 4'-[2-[[ (2R)-2-(3-Fluorophenyl)-2-hydroxyethyl]-  
amino]ethyl]-3-propoxy-1,1'-biphenyl-4-carboxylic acid  
hydrochloride

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.01 (3H, t,  $J=7.4$ Hz), 1.5-1.9 (2H, m),  
2.9-3.4 (6H, m), 4.11 (2H, q,  $J=7.4$ Hz), 4.9-5.1 (1H,  
m), 6.22 (1H, m), 7.1-7.8 (11H, m)

MS  $m/z$ : 438 (M+H)

5

(41) 4'-[(2R)-2-[[ (2R)-2-(3-Fluorophenyl)-2-hydroxyethyl]-  
aminolpropyl]-3-propoxy-1,1'-biphenyl-4-carboxylic acid  
hydrochloride

10 NMR (DMSO- $d_6$ ,  $\delta$ ): 0.99 (3H, t,  $J=7.4$ Hz), 1.10 (3H, d,  
 $J=6.8$ Hz), 1.5-1.9 (2H, m), 2.7-3.4 (5H, m), 4.03 (2H,  
q,  $J=7.4$ Hz), 4.9-5.1 (1H, m), 6.22 (1H, m), 7.1-  
7.8 (11H, m)

MS  $m/z$ : 450 (M-H)

15 (42) 4'-[2-[[ (2R)-2-(3-Fluorophenyl)-2-hydroxyethyl]amino]-  
ethyl]-3-isopropoxy-1,1'-biphenyl-4-carboxylic acid  
hydrochloride

20 NMR (DMSO- $d_6$ ,  $\delta$ ): 1.31 (6H, d,  $J=6.0$ Hz), 2.9-3.4 (6H, m),  
4.81 (1H, m), 4.9-5.1 (1H, m), 6.22 (1H, m), 7.1-  
7.8 (11H, m)

MS  $m/z$ : 438 (M+H)

(43) 4'-[(2R)-2-[[ (2R)-2-(3-fluorophenyl)-2-hydroxyethyl]-  
aminolpropyl]-3-isopropoxy-1,1'-biphenyl-4-carboxylic  
25 acid hydrochloride

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.10 (3H, d,  $J=6.8$ Hz), 1.31 (6H, d,  
 $J=6.0$ Hz), 2.7-3.4 (5H, m), 4.82 (1H, m), 4.9-5.1 (1H,  
m), 6.22 (1H, m), 7.1-7.8 (11H, m)

MS  $m/z$ : 450 (M-H)

30

(44) 3-(Cyclohexyloxy)-4'-[(2R)-2-[[ (2R)-2-(3-fluorophenyl)-  
2-hydroxyethyl]aminolpropyl]-1,1'-biphenyl-4-carboxylic  
acid hydrochloride

35 NMR (DMSO- $d_6$ ,  $\delta$ ): 1.13 (3H, d,  $J=6.8$ Hz), 1.2-2.0 (10H, m),  
2.7-3.4 (5H, m), 4.65 (1H, m), 4.9-5.1 (1H, m),

6.22 (1H, m), 7.1-7.8 (11H, m)

MS m/z: 490 (M-H)

(45) 4'-[2-[[ (2R)-2-(4-Chlorophenyl)-2-hydroxyethyl]amino]-  
ethyl]-3-propoxy-1,1'-biphenyl-4-carboxylic acid  
hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.01 (3H, t, J=7.4Hz), 1.5-1.9 (2H, m),  
2.9-3.4 (6H, m), 4.10 (2H, q, J=7.4Hz), 4.9-5.1 (1H,  
m), 6.28 (1H, m), 7.1-7.8 (11H, m)

MS m/z: 438 (M+H)

(46) 4'-[2-[[ (2R)-2-(4-Chlorophenyl)-2-hydroxyethyl]amino]-  
ethyl]-3-isopropoxy-1,1'-biphenyl-4-carboxylic acid  
hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.29 (6H, d, J=6.0Hz), 2.9-3.4 (6H, m),  
4.84 (1H, m), 4.9-5.1 (1H, m), 6.30 (1H, m), 7.1-  
7.8 (11H, m)

MS m/z: 454 (M+H)

(47) 4'-[(2R)-2-[[ (2R)-2-(4-Chlorophenyl)-2-hydroxyethyl]-  
amino]propyl]-3-propoxy-1,1'-biphenyl-4-carboxylic acid  
hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.00 (3H, t, J=7.4Hz), 1.12 (3H, d,  
J=6.8Hz), 1.5-1.9 (2H, m), 2.7-3.4 (5H, m), 4.03 (2H,  
q, J=7.4Hz), 4.9-5.1 (1H, m), 6.32 (1H, m), 7.1-  
7.8 (11H, m)

MS m/z: 468 (M-H)

(48) 4'-[(2R)-2-[[ (2R)-2-(4-Chlorophenyl)-2-hydroxyethyl]-  
amino]propyl]-3-isopropoxy-1,1'-biphenyl-4-carboxylic  
acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.09 (3H, d, J=6.8Hz), 1.29 (6H, d,  
J=6.0Hz), 2.7-3.4 (5H, m), 4.82 (1H, m), 4.9-5.1 (1H,  
m), 6.32 (1H, m), 7.1-7.8 (11H, m)

MS m/z: 468 (M-H)

(49) 3-Ethoxy-4'-[(2R)-2-[[ (2R)-2-hydroxy-2-(3-pyridyl)-ethyl]amino]propyl]-1,1'-biphenyl-4-carboxylic acid dihydrochloride

5 NMR (DMSO-d<sub>6</sub>, δ): 1.19(3H, d, J=6.8Hz), 1.36(3H, t, J=7.0Hz), 2.7-3.4(5H, m), 4.23(2H, q, J=7.0Hz), 5.1-5.3(1H, m), 6.32(1H, m), 7.2-7.9(8H, m), 8.25(1H, d, J=8Hz), 8.7-8.9(2H, m), 8.94(1H, m), 9.20(1H, m)

10 MS m/z: 421 (M+H)

(50) 4'-[(2R)-2-[[ (2R)-2-Hydroxy-2-(3-pyridyl)ethyl]-amino]propyl]-3-propoxy-1,1'-biphenyl-4-carboxylic acid hydrochloride

15 NMR (DMSO-d<sub>6</sub>, δ): 1.01(3H, t, J=7.4Hz), 1.19(3H, d, J=6.8Hz), 1.5-1.9(2H, m), 2.7-3.4(5H, m), 4.04(2H, q, J=7.4Hz), 5.1-5.3(1H, m), 6.32(1H, m), 7.2-7.9(8H, m), 8.25(1H, d, J=8Hz), 8.7-8.9(2H, m), 8.94(1H, m), 9.20(1H, m)

20 MS m/z: 435 (M+H)

(51) 4'-[(2R)-2-[[ (2R)-2-Hydroxy-2-(3-pyridyl)ethyl]-amino]propyl]-3-isobutoxy-1,1'-biphenyl-4-carboxylic acid dihydrochloride

25 NMR (DMSO-d<sub>6</sub>, δ): 1.01(6H, t, J=6.8Hz), 1.17(3H, d, J=6.8Hz), 1.9-2.1(1H, m), 2.7-3.4(5H, m), 3.93(2H, d, J=6.4Hz), 5.2-5.4(1H, m), 7.2-7.9(8H, m), 8.4(1H, d, J=8Hz), 8.7-8.9(2H, m), 9.09(1H, m), 9.42(1H, m)

30 MS m/z: 449 (M+H)

(52) N-[[4'-[(2R)-2-[[ (2R)-2-Hydroxy-2-(3-pyridyl)ethyl]-amino]propyl]-1,1'-biphenyl-4-yl]carbonyl]-1-phenylmethanesulfonamide dihydrochloride

35 MS m/z: 528 (M-H)

- (53) 4'-[(2R)-2-[[ (2R)-2-(6-Chloro-3-pyridyl)-2-hydroxyethyl]amino]propyl]-3-propoxy-1,1'-biphenyl-4-carboxylic acid dihydrochloride
- 5 NMR (DMSO-d<sub>6</sub>, δ): 1.01(3H, t, J=7.4Hz), 1.12(3H, d, J=6.8Hz), 1.7-1.9(2H, m), 2.7-3.4(5H, m), 4.11(2H, q, J=7.4Hz), 4.9-5.3(1H, m), 7.2-7.8(10H, m), 8.56(1H, s)
- MS m/z: 469 (M+H)
- 10
- (54) 4'-[2-[[ (2R)-2-Hydroxy-2-(3-pyridyl)ethyl]amino]ethyl]-3-isopropoxy-1,1'-biphenyl-4-carboxylic acid dihydrochloride
- 15 NMR (DMSO-d<sub>6</sub>, δ): 1.29(6H, d, J=6.0Hz), 2.9-3.4(6H, m), 4.84(1H, m), 4.9-5.1(1H, m), 7.2-7.5(4H, m), 7.6-7.9(4H, m), 8.2-8.5(1H, m), 8.7-8.9(2H, m), 9.0-9.4(2H, m)
- MS m/z: 421 (M+H)
- 20
- (55) 4'-[2-[[ (2R)-2-Hydroxy-2-(3-pyridyl)ethyl]amino]ethyl]-3-propoxy-1,1'-biphenyl-4-carboxylic acid dihydrochloride
- 25 NMR (DMSO-d<sub>6</sub>, δ): 1.01(3H, t, J=7.4Hz), 1.5-1.9(2H, m), 3.0-3.4(6H, m), 4.11(2H, q, J=7.4Hz), 5.0-5.3(1H, m), 7.2-7.5(4H, m), 7.6-7.9(4H, m), 8.3-8.5(1H, m), 8.7-8.9(2H, m), 9.0-9.4(2H, m)
- MS m/z: 421 (M+H)
- 30
- (56) 3-(Cyclohexyloxy)-4'-[2-[[ (2R)-2-hydroxy-2-(3-pyridyl)ethyl]amino]ethyl]-1,1'-biphenyl-4-carboxylic acid dihydrochloride
- 35 NMR (DMSO-d<sub>6</sub>, δ): 1.0-2.0(10H, m), 2.9-3.4(6H, m), 4.65(1H, m), 5.0-5.3(1H, m), 7.2-7.5(4H, m), 7.6-8.0(4H, m), 8.4-8.6(1H, m), 8.7-8.9(2H, m), 9.0-9.4(2H, m)

MS m/z: 461 (M-H)

- (57) 4'-[2-[[ (2R)-2-(6-Chloro-3-pyridyl)-2-hydroxyethyl]-amino]ethyl]-3-propoxy-1,1'-biphenyl-4-carboxylic acid dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.01 (3H, t, J=7.4Hz), 1.6-1.9 (2H, m), 3.0-3.4 (6H, m), 4.11 (2H, q, J=7.4Hz), 5.0-5.3 (1H, m), 7.1-7.9 (9H, m), 8.46 (1H, s)

MS m/z: 453 (M-H)

- (58) 3-Butyl-4'-[(2R)-2-[[ (2R)-2-hydroxy-2-phenylethyl]-amino]propyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 0.90 (3H, t, J=7.4Hz), 1.0-1.8 (9H, m), 2.8-3.8 (5H, m), 5.0-5.3 (1H, m), 6.3-6.4 (1H, m), 7.2-7.8 (11H, m)

MS m/z: 432 (M+H)

- (59) 3-(3-Butenyl)-4'-[(2R)-2-[[ (2R)-2-hydroxy-2-phenylethyl]amino]propyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride

MS m/z: 430 (M+H)

- (60) 4'-[2-[[ (2R)-2-hydroxy-2-phenylethyl]amino]-2-methylpropyl]-3-isopropoxy-1,1'-biphenyl-4-carboxylic acid hydrochloride

MS m/z: 482 (M+H)

- (61) 4'-[3-[[ (2R)-2-Hydroxy-2-phenylethyl]amino]propyl]-3-isopropoxy-1,1'-biphenyl-4-carboxylic acid hydrochloride

MS m/z: 434 (M+H)

- (62) 4'-[2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-ethyl]-3-isopropoxy-1,1'-biphenyl-4-carboxylic acid



hydrochloride

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.31 (6H, d,  $J=6.0\text{Hz}$ ), 2.8-3.0 (6H, m), 4.79 (1H, q,  $J=6.0\text{Hz}$ ), 4.8-5.0 (1H, m), 6.33 (1H, m), 7.0-7.9 (11H, m)

5 MS  $m/z$ : 454 (M+H)

(63) Ethyl 4'-[2-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-1,1'-biphenyl-3-carboxylate  
10 (+)ESI-MS  $m/z$ : 524 (M+H)<sup>+</sup>

(64) Methyl 3'-[2-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-1,1'-biphenyl-4-carboxylate  
15 (+)ESI-MS  $m/z$ : 510 (M+H)<sup>+</sup>

(65) Methyl 4'-[2-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-2-fluoro-1,1'-biphenyl-4-carboxylate  
20 (+)ESI-MS  $m/z$ : 550 (M+Na)<sup>+</sup>

(66) Methyl 4'-[2-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-3-chloro-1,1'-biphenyl-4-carboxylate  
25 (+)ESI-MS  $m/z$ : 566 (M+Na)<sup>+</sup>

(67) Methyl 4'-[2-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-2'-methoxy-1,1'-biphenyl-4-carboxylate  
30 (+)ESI-MS  $m/z$ : 540 (M+H)<sup>+</sup>

(68) Methyl 4'-[2-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-2'-chloro-1,1'-biphenyl-4-carboxylate  
35 (+)ESI-MS  $m/z$ : 544 (M+H)<sup>+</sup>

- (69) tert-Butyl N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-  
N-[2-[4'-formyl-3'-(1-piperidinyl)-1,1'-biphenyl-4-  
yl]ethyl]carbamate  
5 (+)ESI-MS m/z: 563 (M+H)<sup>+</sup>
- (70) Methyl 4'-[3-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-  
chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,1'-  
biphenyl-4-carboxylate  
10 MS (m/z): 524 (M+H)
- (71) Ethyl 4'-[3-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-  
chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,1'-  
biphenyl-3-carboxylate  
15 MS (m/z): 538 (M+H)
- (72) Methyl 4'-[3-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-  
chlorophenyl)-2-hydroxyethyl]amino]propyl]-3-fluoro-  
1,1'-biphenyl-4-carboxylate  
20 MS (m/z): 542 (M+H)
- (73) Methyl 4'-[3-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-  
chlorophenyl)-2-hydroxyethyl]amino]propyl]-3-methoxy-  
1,1'-biphenyl-4-carboxylate  
25 MS (m/z): 554 (M+H)
- (74) Methyl 4'-[3-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-  
chlorophenyl)-2-hydroxyethyl]amino]propyl]-3-chloro-  
1,1'-biphenyl-4-carboxylate  
30 MS (m/z): 558 (M+H)
- (75) Methyl 4'-[3-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-  
chlorophenyl)-2-hydroxyethyl]amino]propyl]-3-methyl-  
1,1'-biphenyl-4-carboxylate  
35 MS (m/z): 538 (M+H)

- (76) Methyl 3'-[3-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,1'-biphenyl-4-carboxylate  
5 MS (m/z): 523 (M+H)
- (77) Ethyl 3'-[3-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,1'-biphenyl-3-carboxylate  
10 MS (m/z): 538 (M+H)
- (78) Methyl 4'-[2-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(5-chloro-3-pyridyl)-2-hydroxyethyl]amino]ethyl]-1,1'-biphenyl-4-carboxylate  
15 MS (m/z): 511 (M+H)
- (79) tert-Butyl N-[(2R)-2-(6-chloro-3-pyridyl)-2-hydroxyethyl]-N-[(1R)-2-(4'-formyl-3'-phenoxy-1,1'-biphenyl-4-yl)-1-methylethyl]carbamate  
20 MS (m/z): 587 (M+H)
- (80) tert-Butyl N-[2-(4'-formyl-3'-phenoxy-1,1'-biphenyl-4-yl)ethyl]-N-[(2R)-2-hydroxy-2-(3-pyridyl)ethyl]-carbamate  
25 MS (m/z): 539 (M+H)
- (81) Methyl [4'-[2-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-1,1'-biphenyl-4-yl]acetate  
30 MS (m/z): 524 (M+H)
- (82) Methyl [4'-[2-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-1,1'-biphenyl-3-yl]acetate  
35 MS (m/z): 524 (M+H)

- (83) Methyl 4-[4-[(2R)-2-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(6-chloro-3-pyridyl)-2-hydroxyethyl]amino]propyl]-phenyl]-1-naphthoate  
5 MS (m/z): 575 (M+H)
- (84) tert-Butyl N-[(1R)-2-[4'-[(benzoylamino)sulfonyl]-1,1'-biphenyl-4-yl]-1-methylethyl]-N-[(2R)-2-(6-chloro-3-pyridyl)-2-hydroxyethyl]carbamate  
10 MS (m/z): 650 (M+H)
- (85) tert-Butyl N-[2-[4'-formyl-3'-(1-piperidinyl)-1,1'-biphenyl-4-yl]ethyl]-N-[(2R)-2-hydroxy-2-phenylethyl]-carbamate  
15 MS (m/z): 529 (M+H)
- (86) 4'-[2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-ethyl]-3-(2-methoxyethoxy)-1,1'-biphenyl-4-carboxylic acid hydrochloride  
20 MS (m/z): 470 (M+H)
- (87) 3-(2-Ethoxyethoxy)-4'-[2-[[ (2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride  
25 MS (m/z): 484 (M+H)
- (88) 4'-[2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-ethyl]-3-propyl-1,1'-biphenyl-4-carboxylic acid hydrochloride  
30 MS (m/z): 438 (M+H)
- (89) 4'-[2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-ethyl]-3-propoxy-1,1'-biphenyl-4-carboxylic acid hydrochloride  
35 MS (m/z): 454 (M+H)

- (90) 4'-[2-[[ (2R)-2-Hydroxy-2-phenylethyl]amino]ethyl]-3-(2-methoxyethoxy)-1,1'-biphenyl-4-carboxylic acid hydrochloride  
 5 NMR (DMSO-d<sub>6</sub>, δ): 2.8-3.0 (6H, m), 3.32 (3H, s), 3.70 (2H, m), 4.29 (2H, m), 4.8-5.0 (1H, m), 6.33 (1H, m), 7.0-7.9 (12H, m)  
 MS m/z: 436 (M+H)
- 10 (91) 3-(2-Ethoxyethoxy)-4'-[2-[[ (2R)-2-hydroxy-2-phenylethyl]amino]ethyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride  
 MS m/z: 450 (M+H)
- 15 (92) 3-[2-(Dimethylamino)ethoxy]-4'-[2-[[ (2R)-2-hydroxy-2-phenylethyl]amino]ethyl]-1,1'-biphenyl-4-carboxylic acid dihydrochloride  
 NMR (DMSO-d<sub>6</sub>, δ): 1.12 (3H, d, J=6.5Hz), 2.8-3.6 (7H, m), 2.88 (6H, s), 4.58 (2H, m), 4.8-5.0 (1H, m),  
 20 6.33 (1H, m), 7.0-7.9 (12H, m)  
 MS m/z: 462 (M+H)
- (93) 4'-[2-[[ (1S,2R)-2-Hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]-3-isopropoxy-1,1'-biphenyl-4-carboxylic acid hydrochloride  
 25 NMR (DMSO-d<sub>6</sub>, δ): 0.98 (3H, d, J=6.6Hz), 1.31 (6H, d, J=6.0Hz), 2.8-3.5 (5H, m), 4.79 (1H, q, J=6.0Hz), 5.0-5.2 (1H, m), 6.0 (1H, m), 6.7-7.9 (11H, m)  
 MS m/z: 450 (M+H)
- 30

### Example 33

To the mixture of 4'-[2-[[ (2R)-2-phenyl-2-hydroxyethyl]amino]ethyl]-1,1'-biphenyl-4-nitrile (100 mg) in DMF (N,N-dimethylformamide) (10 ml) were added sodium  
 35 azide (30 mg) and ammonium chloride (30 mg), and stirred at

120°C for 12 hours. The resulting mixture was poured into a mixture of ethyl acetate and water, and the organic layer was washed with brine. After the solvent was evaporated under pressure, the residue was purified by column  
 5 chromatography on silica gel to give the corresponding tetrazole. The obtained tetrazole was diluted with 6N hydrogen chloride in 1,4-dioxane (10 ml) and the mixture was allowed to keep at the room temperature for 4 hours. The mixture was evaporated under reduced pressure and the  
 10 obtained solid was washed with ether to give  
 (1R)-2-[[[(1R)-1-methyl-2-[4'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]ethyl]amino]-1-phenylethanol hydrochloride (25 mg).

15 NMR (DMSO-d<sub>6</sub>, δ): 1.14(3H, d, J=6.4Hz), 2.6-3.2(5H, m),  
 3.93(2H, d, J=6.6Hz), 4.9-5.1(1H, m), 6.24(1H, m),  
 7.2-7.5(7H, m), 7.77(2H, d, J=8.0Hz), 7.94(2H, d,  
 J=8.0Hz), 8.15(2H, d, J=8.0Hz)

MS m/z: 400 (M+H)

#### 20 Example 34

The following compounds were obtained according to a similar manner to that of Example 30.

25 (1) 4'-[3-[N-(tert-Butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,1'-biphenyl-4-carboxylic acid

MS (m/z): 510 (M+H)

30 (2) 4'-[3-[N-(tert-Butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,1'-biphenyl-3-carboxylic acid

MS (m/z): 510 (M+H)

35 (3) 4'-[3-[N-(tert-Butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-3-fluoro-

1,1'-biphenyl-4-carboxylic acid

MS (m/z): 528 (M+H)

- 5 (4) 4'-[3-[N-(tert-Butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-3-methoxy-1,1'-biphenyl-4-carboxylic acid  
MS (m/z): 540 (M+H)
- 10 (5) 4'-[3-[N-(tert-Butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-3-chloro-1,1'-biphenyl-4-carboxylic acid  
MS (m/z): 544 (M+H)
- 15 (6) 4'-[3-[N-(tert-Butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-3-methyl-1,1'-biphenyl-4-carboxylic acid  
MS (m/z): 524 (M+H)
- 20 (7) 3'-[3-[N-(tert-Butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,1'-biphenyl-4-carboxylic acid  
MS (m/z): 523 (M+H)
- 25 (8) 3'-[3-[N-(tert-Butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,1'-biphenyl-3-carboxylic acid  
MS (m/z): 510 (M+H)
- 30 (9) [4'-[(2R)-2-[N-(tert-Butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,1'-biphenyl-4-yl]acetic acid  
MS (m/z): 524 (M+H)
- 35 (10) 4'-[2-[N-(tert-Butoxycarbonyl)-N-[(2R)-2-(5-chloro-3-pyridyl)-2-hydroxyethyl]amino]ethyl]-1,1'-biphenyl-4-

carboxylic acid

MS (m/z): 497 (M+H)

(11) 4'-[2-[N-(tert-Butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-1,1'-biphenyl-4-yl]acetic acid

MS (m/z): 510 (M+H)

(12) 4-[4-[N-(2R)-2-[N-(tert-Butoxycarbonyl)-N-[(2R)-2-(6-chloro-3-pyridyl)-2-hydroxyethyl]amino]propyl]phenyl]-1-naphthoic acid

MS (m/z): 561 (M+H)

#### Example 35

The following compounds were obtained according to a similar manner to that of Example 27.

(1) 4'-[3-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-propyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.70-2.10 (2H, m), 2.60-3.40 (6H, m), 4.90-5.10 (1H, m), 7.40-7.60 (6H, m), 7.70-7.90 (4H, m), 8.10 (1H, d, J=8Hz)

MS (m/z): 410 (M+H)

(2) 4'-[3-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,1'-biphenyl-3-carboxylic acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.80-2.10 (2H, m), 2.60-3.40 (6H, m), 4.90-5.10 (1H, m), 7.30-7.60 (9H, m), 7.80-7.90 (1H, m), 8.10 (1H, s)

MS (m/z): 410 (M+H)

(3) 4'-[3-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-propyl]-3-fluoro-1,1'-biphenyl-4-carboxylic acid hydrochloride



NMR (DMSO- $d_6$ ,  $\delta$ ): 1.80-2.10 (2H, m), 2.60-3.40 (6H, m),  
4.90-5.10 (1H, m), 7.30-7.80 (10H, m), 8.00 (1H, t,  
J=8Hz)

MS (m/z): 428 (M+H)

5

- (4) 4'-[3-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-  
propyl]-3-methoxy-1,1'-biphenyl-4-carboxylic acid  
hydrochloride

10 NMR (DMSO- $d_6$ ,  $\delta$ ): 1.80-2.10 (2H, m), 2.60-3.40 (6H, m),  
4.00 (3H, s), 4.90-5.10 (1H, m), 7.30-7.50 (8H, m),  
7.70-7.80 (3H, m)

MS (m/z): 440 (M+H)

- 15 (5) 3-Chloro-4'-[3-[[ (2R)-2-(3-chlorophenyl)-2-  
hydroxyethyl]amino]propyl]-1,1'-biphenyl-4-carboxylic  
acid hydrochloride

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.80-2.10 (2H, m), 2.60-3.40 (6H, m),  
4.90-5.10 (1H, m), 7.30-7.60 (6H, m), 7.70-7.90 (5H,  
m)

20 MS (m/z): 444 (M+H)

- (6) 4'-[3-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-  
propyl]-3-methyl-1,1'-biphenyl-4-carboxylic acid  
hydrochloride

25 NMR (DMSO- $d_6$ ,  $\delta$ ): 1.80-2.10 (2H, m), 2.60 (3H, s), 2.60-  
3.40 (6H, m), 4.90-5.10 (1H, m), 7.30-7.60 (10H, m),  
7.90 (1H, s)

MS (m/z): 424 (M+H)

- 30 (7) 3'-[3-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-  
propyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.80-2.10 (2H, m), 2.60-3.40 (6H, m),  
4.90-5.10 (1H, m), 7.30-7.60 (8H, m), 7.80 (2H, d,  
J=8Hz), 8.10 (2H, d, J=8Hz)

35 MS (m/z): 410 (M+H)

- (8) 3'-[3-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-propyl]-1,1'-biphenyl-3-carboxylic acid hydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.80-2.10 (2H, m), 2.60-3.40 (6H, m),  
5 4.90-5.10 (1H, m), 7.30-7.60 (9H, m), 7.80-7.90 (2H, m), 8.20 (1H, s)  
MS (m/z): 410 (M+H)
- (9) [4'-[(2R)-2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]propyl]-1,1'-biphenyl-4-yl]acetic acid  
10 hydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.05 (3H, d, J=6Hz), 2.80-3.60 (7H, m),  
5.00-5.15 (1H, m), 7.20-7.70 (12H, m)  
MS (m/z): 424 (M+H)
- (10) 4'-[2-[[ (2R)-2-(5-Chloro-3-pyridyl)-2-hydroxyethyl]-amino]ethyl]-1,1'-biphenyl-4-carboxylic acid  
15 dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 3.10-3.40 (6H, m), 5.00-5.10 (1H, m),  
20 7.40-8.10 (9H, m), 7.70-7.80 (2H, m)  
MS (m/z): 397 (M+H)
- (11) 4'-[(2R)-2-[[ (2R)-2-Hydroxy-2-(3-pyridyl)ethyl]-amino]propyl]-3-phenoxy-1,1'-biphenyl-4-carboxylic acid  
25 dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.13 (3H, d, J=6Hz), 2.70-2.80 (1H, m),  
2.80-3.60 (4H, m), 5.30-5.40 (1H, m), 6.90-7.60 (7H, m), 7.90-8.00 (2H, m), 8.50-8.60 (1H, m), 8.80-  
8.90 (2H, m)  
30 MS (m/z): 469 (M+H)
- (12) 4'-[2-[[ (2R)-2-Hydroxy-2-(3-pyridyl)ethyl]amino]-ethyl]-3-phenoxy-1,1'-biphenyl-4-carboxylic acid  
35 dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 3.00-3.50 (6H, m), 5.20-5.30 (1H, m),

7.00-7.70 (7H, m), 7.90-8.00 (2H, m), 8.40-8.50 (1H, m), 8.80-8.90 (2H, m)

MS (m/z): 455 (M+H)

- 5 (13) [4'-[2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-ethyl]-1,1'-biphenyl-4-yl]acetic acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 2.90-3.40 (6H, m), 3.62 (2H, s), 4.90-5.10 (1H, m), 7.30-7.70 (12H, m)

MS (m/z): 410 (M+H)

10

- (14) N-Benzoyl-4'-[(2R)-2-[[ (2R)-2-hydroxy-2-(3-pyridyl)-ethyl]amino]propyl]-1,1'-biphenyl-4-sulfonamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.01 (3H, d, J=6Hz), 2.60-3.60 (5H, m), 5.00-5.15 (1H, m), 7.20-8.10 (13H, m), 8.30-8.40 (1H, m), 8.70-8.80 (2H, m)

15

MS (m/z): 516 (M+H)

- 20 (15) 4'-[2-[[ (2R)-2-Hydroxy-2-phenylethyl]amino]ethyl]-3-(1-piperidinyl)-1,1'-biphenyl-4-carboxylic acid dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.50-1.80 (6H, d, m), 3.00-3.40 (10H, m), 5.00-5.10 (1H, m), 7.20-7.50 (7H, m), 7.70-7.80 (3H, m), 8.10-8.20 (2H, m)

25

MS (m/z): 445 (M+H)

### Example 36

The following compounds were obtained according to a similar manner to that of Example 21.

30

- (1) Methyl 4'-[2-[[ (2R)-2-(6-chloro-3-pyridyl)-2-hydroxyethyl]amino]ethyl]-1,1'-biphenyl-4-carboxylate

MS (m/z): 410 (M+H)

35

- (2) Methyl [4'-[(2R)-2-[[ (2R)-2-(3-chlorophenyl)-2-

hydroxyethyl]amino]propyl]-1,1'-biphenyl-4-yl]acetate

MS (m/z): 438 (M+H)

(3) Ethyl 5-[4-[(2R)-2-[[ (2R)-2-(6-chloro-3-pyridyl)-2-hydroxyethyl]amino]propyl]phenyl]-1-naphthoate

MS (m/z): 489 (M+H)

(4) Methyl 4'-[2-[[ (2R)-2-(4-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-1,1'-biphenyl-4-carboxylate

MS (m/z): 410 (M+H)

(5) Ethyl 6-[4-[2-[N-benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]nicotinate

(+)ESI-MS m/z: 515 (M+H)<sup>+</sup>

(6) Methyl 4'-[2-[N-benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-2,6-dimethyl-1,1'-biphenyl-4-carboxylate

(+)ESI-MS m/z: 528 (M+H)<sup>+</sup>

### Example 37

Under nitrogen to a solution of methyl 4'-[2-[[ (2R)-2-(6-chloro-3-pyridyl)-2-hydroxyethyl]amino]ethyl]-1,1'-biphenyl-4-carboxylate (110 mg) in tetrahydrofuran (10 ml)

was added 1M methylzinc chloride in tetrahydrofuran (0.8 ml) and tetrakis(triphenylphosphine)palladium (15.5 mg) at room temperature. The mixture was stirred at 80°C for 24 hours, and then poured into an aqueous solution (60 ml) of ethylenediaminetetraacetic acid (1 g). The resulting

mixture was neutralized with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel

(chloroform:methanol = 100:1) to give methyl 4'-[2-[[ (2R)-2-

hydroxy-2-(6-methyl-3-pyridyl)ethyl]amino]ethyl]-1,1'-biphenyl-4-carboxylate (41 mg) as a colorless oil.

MS (m/z): 391 (M+H)

### 5 Example 38

The following compounds were obtained by alkaline hydrolysis of each ester thereof in a conventional manner.

(1) Sodium 4'-[2-[[ (2R)-2-hydroxy-2-(6-methyl-3-pyridyl)ethyl]amino]ethyl]-1,1'-biphenyl-4-carboxylate  
 10 NMR (DMSO-d<sub>6</sub>, δ): 2.50(3H, s), 2.60-2.90(6H, m), 4.60-4.70(1H, m), 7.10-7.40(3H, m), 7.50-7.70(5H, m), 7.90(1H, d, J=8Hz), 8.40(1H, s)

15 (2) Sodium 4'-[2-[[ (2R)-2-(6-chloro-3-pyridyl)-2-hydroxyethyl]amino]ethyl]-1,1'-biphenyl-4-carboxylate  
 NMR (DMSO-d<sub>6</sub>, δ): 2.80-3.80(6H, m), 4.90(1H, t, J=6Hz), 7.10-7.90(8H, m), 7.98(2H, d, J=8Hz), 8.30(1H, d, J=2Hz)

20 MS (m/z): 397 (M+H)

(3) Sodium 4'-[2-[[ (2R)-2-(4-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-1,1'-biphenyl-4-carboxylate  
 NMR (DMSO-d<sub>6</sub>, δ): 2.70-3.50(6H, m), 4.50-4.60(1H, m),  
 25 7.10-7.60(8H, m), 7.94(2H, d, J=8Hz)

MS (m/z): 396 (M+H)

### Example 39

The following compounds were obtained according to a similar manner to that of Preparation 29.

(1) Methyl [4'-[(2R)-2-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,1'-biphenyl-4-yl]acetate

35 MS (m/z): 538 (M+H)

(2) Ethyl 5-[4-[(2R)-2-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(6-chloro-3-pyridyl)-2-hydroxyethyl]amino]propyl]-phenyl]-1-naphthoate

5 MS (m/z): 589 (M+H)

#### Example 40

The following compounds were obtained according to a similar manner to that of Example 18.

10

(1) [4'-[2-[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-ethyl]-1,1'-biphenyl-3-yl]acetic acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 2.80-3.40(6H, m), 3.65(2H, s), 4.90-5.10(1H, m), 7.20-7.70(12H, m)

15

MS (m/z): 408 (M-H)

(2) 4'-[2-[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-ethyl]-1,1'-biphenyl-3-carboxylic acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 3.01-3.29(6H, m), 4.97-5.02(1H, m), 6.34(1H, br), 6.90(1H, m), 7.71-7.48(9H, m), 7.89-7.95(2H, m), 8.18(1H, d, J=1.5Hz), 8.96(1H, br)

20

(-)ESI-MS m/z: 394 (M-HCl-H)<sup>-</sup>

(3) 3-[2-[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-ethyl]-6H-benzo[c]chromene-8-carboxylic acid

25

hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 3.00-3.28(6H, m), 4.96-5.01(1H, m), 5.20(2H, s), 6.34(1H, br), 6.94-7.03(2H, m), 7.34-7.47(4H, m), 7.86-7.94(4H, m), 8.94(1H, br)

30

(-)ESI-MS m/z: 422 (M-HCl-H)<sup>-</sup>

(4) 2-[2-[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-ethyl]-6H-benzo[c]chromene-8-carboxylic acid

35

hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 3.00-3.26(6H, m), 5.03-5.07(1H, m),

5.19(2H, s), 6.38(1H, br), 6.99(1H, d, J=8.2Hz),  
7.20-7.25(2H, m), 7.35-7.48(4H, m), 7.85-7.98(4H,  
m), 9.10(1H, br)

(-)ESI-MS m/z: 422 (M-HCl-H)<sup>-</sup>

5

- (5) 6-[4-[2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-  
amino]ethyl]phenyl]nicotinic acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 3.08-3.24(6H, m), 5.00-5.07(1H, br),  
7.34-7.47(6H, m), 8.09-8.17 (3H, m), 8.31-8.38(1H,  
m), 8.98(1H, br), 9.12-9.16(1H, m), 9.30(1H, br)

10

(-)ESI-MS m/z: 395 (M-HCl-H)<sup>-</sup>

- (6) 3'-[2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-  
ethyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride

15

NMR (DMSO-d<sub>6</sub>, δ): 3.01-3.28(6H, m), 4.97-5.02(1H, m),  
6.34(1H, br), 7.34-7.48(6H, m), 7.62-7.65(2H, m),  
7.78-7.83(2H, m), 8.01-8.05(2H, m), 8.96(1H, br)

(-)ESI-MS m/z: 394 (M-HCl-H)<sup>-</sup>

20

- (7) 4'-[2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-  
ethyl]-2-fluoro-1,1'-biphenyl-4-carboxylic acid  
hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 3.01-3.28(6H, m), 5.02-5.05(1H, m),  
6.38(1H, br), 7.37-7.87(11H, m), 9.10(1H, br)

25

(-)ESI-MS m/z: 412 (M-HCl-H)<sup>-</sup>

- (8) 4'-[2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-  
ethyl]-2,6-dimethyl-1,1'-biphenyl-4-carboxylic acid  
hydrochloride

30

NMR (DMSO-d<sub>6</sub>, δ): 2.00(6H, m), 3.06-3.11(6H, m), 4.98-  
5.04(1H, m), 6.36-6.85(1H, br), 7.11-7.15(2H,  
m), 7.35-7.49(6H, m), 7.70-7.72(2H, m), 9.06(1H,  
br)

(-)ESI-MS m/z: 422 (M-HCl-H)<sup>-</sup>

35

- (9) 3-Chloro-4'-[2-[[ (2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride  
 NMR (DMSO-d<sub>6</sub>, δ): 3.01-3.28 (6H, m), 5.00-5.04 (1H, m),  
 5 6.36 (1H, br), 7.35-7.47 (6H, m), 7.70-7.91 (5H, m),  
 9.07 (1H, br)  
 (-)ESI-MS m/z: 428 (M-HCl-H)<sup>-</sup>
- (10) 4'-[2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-ethyl]-2'-methoxy-1,1'-biphenyl-4-carboxylic acid hydrochloride  
 NMR (DMSO-d<sub>6</sub>, δ): 3.03-3.27 (6H, m), 3.80 (3H, s), 5.03-  
 5.07 (1H, m), 6.38 (1H, br), 6.96 (1H, d, J=7.9Hz),  
 7.06 (1H, s), 7.29-7.48 (5H, m), 7.58 (1H, d,  
 15 J=8.3Hz), 7.96 (1H, d, J=8.3Hz), 9.13-9.18 (1H, br)  
 (-)ESI-MS m/z: 424 (M-HCl-H)<sup>-</sup>
- (11) 2'-Chloro-4'-[2-[[ (2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride  
 NMR (DMSO-d<sub>6</sub>, δ): 3.00-3.27 (6H, m), 5.01-5.07 (1H, m),  
 6.37-6.39 (1H, br), 6.96 (1H, d, J=7.9Hz), 7.34-  
 7.57 (9H, m), 8.04 (2H, d, J=8.3Hz), 9.04-  
 9.30 (1H, br)  
 25 (-)ESI-MS m/z: 428 (M-HCl-H)<sup>-</sup>
- (12) 4'-[2-[[ (2R)-2-Hydroxy-2-phenylethyl]amino]ethyl]-3-(isopropylthio)-1,1'-biphenyl-4-carboxylic acid hydrochloride  
 NMR (DMSO-d<sub>6</sub>, δ): 1.31 (6H, d, J=6.5Hz), 2.99-3.33 (6H,  
 30 m), 3.69-3.82 (1H, m), 4.96-5.00 (1H, m), 6.22 (1H, m),  
 7.30-7.92 (12H, m)  
 (-)ESI-MS m/z: 434 (M-HCl-H)<sup>-</sup>
- (13) 4'-[2-[[ (2R)-2-Hydroxy-2-phenylethyl]amino]ethyl]-3-



(isopropylsulfonyl)-1,1'-biphenyl-4-carboxylic acid  
hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.25 (6H, d, J=6.8Hz), 2.99-3.33 (6H,  
m), 3.94-4.08 (1H, m), 4.96-5.00 (1H, m), 6.22 (1H,  
m), 7.27-8.12 (12H, m)  
(-)ESI-MS m/z: 466 (M-HCl-H)<sup>-</sup>

#### Example 41

The following compounds were obtained according to a  
similar manner to that of Example 14 followed by a similar  
manner to that of Example 18.

(1) 4'-[2-[[ (2R)-2-Hydroxy-2-phenylethyl]amino]ethyl]-3-  
isobutyl-1,1'-biphenyl-4-carboxylic acid hydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 0.89(6H, d, J=8Hz), 1.80-2.00(1H, m),  
2.90-3.40(8H, m), 4.90-5.10(1H, m), 7.30-7.80(12H,  
m)  
MS (m/z): 418 (M+H)

(2) 4'-[(2R)-2-[[ (2R)-2-Hydroxy-2-phenylethyl]amino]-  
propyl]-3-isobutyl-1,1'-biphenyl-4-carboxylic acid  
hydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 0.89(7H, d, J=6Hz), 1.21(3H, d,  
J=6Hz), 1.80-1.90(1H, m), 2.70-3.60(7H, m), 5.00-  
5.10(1H, m), 7.20-7.80(12H, m)  
MS (m/z): 432 (M+H)

(3) 4'-[2-[[ (2R)-2-Hydroxy-2-phenylethyl]amino]ethyl]-3-  
isopropyl-1,1'-biphenyl-4-carboxylic acid hydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.20(3H, d, J=7Hz), 2.90-3.40(6H, m),  
3.80-3.90(1H, m), 4.90-5.00(1H, m), 7.20-7.80(12H,  
m)  
MS (m/z): 404 (M+H)

(4) 4'-[2-[[ (2R)-2-Hydroxy-2-phenylethyl]amino]ethyl]-3-

phenyl-1,1'-biphenyl-4-carboxylic acid hydrochloride  
 NMR (DMSO-d<sub>6</sub>, δ): 2.90-3.40 (6H, m), 4.95-5.10 (1H, m),  
 7.30-7.80 (17H, m)  
 MS (m/z): 438 (M+H)

5

- (5) 4'-[2-[[ (2R)-2-Hydroxy-2-phenylethyl]amino]ethyl]-3-propyl-1,1'-biphenyl-4-carboxylic acid hydrochloride  
 NMR (DMSO-d<sub>6</sub>, δ): 0.90-1.05 (3H, m), 1.50-1.70 (2H, m),  
 2.80-3.40 (8H, m), 4.90-5.05 (1H, m), 7.20-7.80 (12H,  
 10 m)  
 MS (m/z): 404 (M+H)

15

- (6) 4'-[(2R)-2-[[ (2R)-2-Hydroxy-2-phenylethyl]amino]-propyl]-3-propyl-1,1'-biphenyl-4-carboxylic acid  
 hydrochloride  
 NMR (DMSO-d<sub>6</sub>, δ): 0.80-1.70 (8H, m), 2.70-3.20 (7H, m),  
 5.00-5.15 (1H, m), 7.10-7.90 (12H, m)  
 MS (m/z): 418 (M+H)

20

- (7) 4'-[(2R)-2-[[ (2R)-2-Hydroxy-2-phenylethyl]amino]-propyl]-3-isopropyl-1,1'-biphenyl-4-carboxylic acid  
 hydrochloride  
 NMR (DMSO-d<sub>6</sub>, δ): 1.05-1.10 (9H, m), 2.05-2.15 (1H, m),  
 2.80-3.60 (5H, m), 5.00-5.15 (1H, m), 7.20-7.80 (12H,  
 25 m)  
 MS (m/z): 418 (M+H)

30

- (8) 4'-[(2R)-2-[[ (2R)-2-Hydroxy-2-(3-pyridyl)ethyl]-amino]propyl]-3-phenyl-1,1'-biphenyl-4-carboxylic acid  
 dihydrochloride  
 NMR (DMSO-d<sub>6</sub>, δ): 1.15 (3H, d, J=6Hz), 2.80-2.90 (1H, m),  
 3.20-3.60 (4H, m), 5.10-5.20 (1H, m), 7.30-7.90 (13H,  
 m), 8.30-8.40 (1H, m), 8.70-8.90 (2H, m)  
 MS (m/z): 453 (M+H)

35

- (9) 4'-[2-[[ (2R)-2-Hydroxy-2-phenylethyl]amino]ethyl]-3-phenyl-1,1'-biphenyl-4-carboxylic acid hydrochloride  
 NMR (DMSO-d<sub>6</sub>, δ): 3.00-3.60 (6H, m), 5.20-5.30 (1H, m),  
 7.20-7.90 (13H, m), 8.30-8.40 (1H, m), 8.70-8.80 (2H,  
 5 m)  
 MS (m/z): 439 (M+H)

#### Example 42

The following compounds were obtained by conversion of  
 10 an amino protective group from each corresponding amino  
 protective group of benzyl in a conventional manner.

- (1) Ethyl 6-[4-[2-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-  
 chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-  
 15 nicotinate  
 (+)ESI-MS m/z: 547 (M+Na)<sup>+</sup>
- (2) Methyl 4'-[2-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-  
 chlorophenyl)-2-hydroxyethyl]amino]ethyl]-2,6-dimethyl-  
 20 1,1'-biphenyl-4-carboxylate  
 (+)ESI-MS m/z: 560 (M+Na)<sup>+</sup>

#### Example 43

The following compound was obtained according to a  
 25 similar manner to that of Example 55.

tert-Butyl N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-  
 N-[2-(3'-hydroxy-1,1'-biphenyl-4-yl)ethyl]carbamate  
 30 (+)ESI-MS m/z: 468 (M+H)<sup>+</sup>

#### Example 44

The following compound was obtained by a replacement  
 reaction of the object compound of Example 43 with tert-  
 butyl 2-bromoacetate in a conventional manner.

tert-Butyl [[4'-[2-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-1,1'-biphenyl-3-yl]oxy]acetate

(+)ESI-MS m/z: 582 (M+H)<sup>+</sup>

5

#### Example 45

The following compound was obtained by elimination of two amino protective groups of the object compound of Example 44 in a conventional manner.

10

[[4'-[2-[[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]ethyl]-1,1'-biphenyl-3-yl]oxy]acetic acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 3.00-3.27(6H,m), 4.76(2H,s), 5.01-  
15 5.05(1H,m), 6.36(1H,br), 6.90(1H,m), 7.15-  
7.48(9H,m), 7.64(2H,d,J=8.0Hz), 9.09-9.21(1H,br)  
(-)ESI-MS m/z: 424 (M-HCl-H)<sup>-</sup>

#### Example 46

20 The following compound was obtained according to a similar manner to that of Preparation 61.

Methyl 4-bromo-3-[[4-[2-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-  
25 phenoxy]methyl]benzoate

(+)ESI-MS m/z: 617, 619 (M+H)<sup>+</sup>

#### Example 47

30 The following compound was obtained according to a similar manner to that of Example 20.

tert-Butyl N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-N-[2-[4'-formyl-3'-(1-piperidiny)]-1,1'-biphenyl-4-yl]ethyl]carbamate

35 NMR (DMSO-d<sub>6</sub>, δ): 1.71-2.00(6H, m), 3.09-3.20(6H,m),

3.47-3.59 (4H, br), 5.06-5.10 (1H, m), 7.28-7.48 (6H, m), 7.82-7.89 (3H, m), 8.12-8.21 (2H, m)  
 (-)ESI-MS m/z: 474 (M-HCl-H)<sup>-</sup>

#### 5 Example 48

The following compound was obtained according to a similar manner to that of Preparation 28.

Methyl 3-[2-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-6H-benzo[c]chromene-8-carboxylate  
 (+)ESI-MS m/z: 538 (M+H)<sup>+</sup>

#### Example 49

15 The following compound was obtained according to a similar manner to that of Preparation 62.

Methyl 2-[2-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-6H-benzo[c]chromene-8-carboxylate  
 20 (+)ESI-MS m/z: 560 (M+Na)<sup>+</sup>

#### Example 50

25 The following compounds were obtained according to a similar manner to that of Example 1.

(1) 4'-[2-[N-(tert-Butoxycarbonyl)-N-[(2R)-2-hydroxy-2-(3-pyridyl)ethyl]amino]ethyl]-3-phenoxy-1,1'-biphenyl-4-carboxylic acid  
 30 MS (m/z): 555 (M+H)

(2) 4'-[2-[N-(tert-Butoxycarbonyl)-N-[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]-3-(1-piperidinyl)-1,1'-biphenyl-4-carboxylic acid  
 35 MS (m/z): 545 (M+H)

Example 51

The following compound was obtained according to a similar manner to that of Example 1 followed by a similar manner to that of Example 25.

4'-[(2R)-2-[N-(tert-Butoxycarbonyl)-N-[(2R)-2-hydroxy-2-(3-pyridyl)ethyl]amino]propyl]-3-phenoxy-1,1'-biphenyl-4-carboxylic acid

MS (m/z): 569 (M+H)

Example 52

The following compound was obtained according to a similar manner to that of Example 25 followed by a similar manner to that of Example 18.

5-[4-[(2R)-2-[[ (2R)-2-Hydroxy-2-(3-pyridyl)ethyl]-amino]propyl]phenyl]-1-naphthoic acid dihydrochloride

MS (m/z): 426 (M+H)

Example 53

The following compound was obtained according to a similar manner to that of Example 25 followed by a similar manner to that of Example 27.

4-[4-[(2R)-2-[[ (2R)-2-Hydroxy-2-(3-pyridyl)ethyl]-amino]propyl]phenyl]-1-naphthoic acid dihydrochloride

MS (m/z): 427 (M+H)

Example 54

The following compound was obtained according to a similar manner to that of Example 25.

tert-Butyl N-[(1R)-2-[4'-[(benzoylamino)sulfonyl]-1,1'-biphenyl-4-yl]-1-methylethyl]-N-[(2R)-2-hydroxy-2-(3-

pyridyl)ethyl]carbamate

MS (m/z): 616 (M+H)

#### Example 55

5 The following compound was obtained according to a similar manner to that of Example 7.

Methyl 4'-[2-[N-(tert-butoxycarbonyl)-N-[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]-3-(isopropylthio)-1,1'-  
10 biphenyl-4-carboxylate

(+)ESI-MS (m/z): 572 (M+Na)<sup>+</sup>

#### Example 56

To a solution of methyl 4'-[2-[N-(tert-butoxycarbonyl)-  
15 N-[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]-3-(isopropylthio)-1,1'-biphenyl-4-carboxylate (338 mg) in chloroform (8 ml) and N,N-dimethylformamide (4 ml) was added m-chloroperbenzoic acid (594 mg) at room temperature and the mixture was stirred at the same temperature for 1 hour. To  
20 the mixture was added water and extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give methyl 4'-[2-[N-(tert-  
25 butoxycarbonyl)-N-[(2R)-2-hydroxy-2-phenylethyl]amino]-ethyl]-3-(isopropylsulfonyl)-1,1'-biphenyl-4-carboxylate (340 mg).

(+)ESI-MS m/z: 604 (M+Na)<sup>+</sup>

#### 30 Preparation 71

To a solution of (2R)-N-benzyl-N-[2-(4-bromophenyl)-ethyl]-2-[[tert-butyl(dimethyl)silyl]oxy]-2-(3-chlorophenyl)ethanamine (2.1 g) in tetrahydrofuran (25 ml) was added a solution of butyllithium in hexane (1.59M, 2.83  
35 ml) dropwise at -70°C under nitrogen and the mixture was

stirred at -70°C for 30 minutes. To the reaction mixture was added 4-[[tert-butyl(dimethyl)silyl]oxy]benzaldehyde (977 mg) at -70°C, and the mixture was stirred at -70°C for 1 hour. The mixture was allowed to warm to room temperature and partitioned between ethyl acetate and water. The organic layer was separated, washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 10/1) to give [4-[2-[N-benzyl-N-[(2R)-2-[[tert-butyl(dimethyl)silyl]oxy]-2-(3-chlorophenyl)-ethyl]amino]ethyl]phenyl][4-[[tert-butyl(dimethyl)silyl]oxy]phenyl]methanol (1.1 g).

(+)ESI-MS m/z: 716 (M+H)<sup>+</sup>

#### Preparation 72

To a solution of (1R)-2-[[2-(4-bromophenyl)ethyl]-amino]-1-(3-chlorophenyl)ethanol (5.1 g) and imidazole (2.9 g) in N,N-dimethylformamide (30 ml) was added tert-butyl(dimethyl)silyl chloride (5.85 g) and the mixture was stirred at 40°C for 24 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water, 5% acetic acid solution, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure to give a crude product. To a solution of the product in tetrahydrofuran (80 ml) and triethylamine (2.0 ml) was added di-tert-butyl dicarbonate (3.14 g), and the mixture was stirred at room temperature for 3 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 20/1) to give tert-butyl N-[2-(4-bromophenyl)ethyl]-N-[(2R)-2-[[tert-butyl(dimethyl)-



silyl]oxy]-2-(3-chlorophenyl)ethyl]carbamate (5.0 g).

(+)ESI-MS  $m/z$ : 568 (M+H)<sup>+</sup>

### Preparation 73

5 To a solution of tert-butyl N-[2-(4-bromophenyl)-ethyl]-N-[(2R)-2-[[tert-butyl(dimethyl)silyl]oxy]-2-(3-chlorophenyl)ethyl]carbamate (880 mg) in tetrahydrofuran (13 ml) was added a solution of butyllithium in hexane (1.59M, 1.07 ml) dropwise at -70°C under nitrogen and the mixture  
10 was stirred at -70°C for 30 minutes. To the reaction mixture was added 4-[[tert-butyl(dimethyl)silyl]oxy]-N-methoxy-N-methylbenzamide (480 mg) at -70°C, and the mixture was stirred at -70°C for 1 hour. The mixture was allowed to warm to room temperature and partitioned between ethyl  
15 acetate and water. The organic layer was separated, washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 10/1) to give tert-butyl N-[2-  
20 [4-[4-[[tert-butyl(dimethyl)silyl]oxy]benzoyl]phenyl]ethyl]-N-[(2R)-2-[[tert-butyl(dimethyl)silyl]oxy]-2-(3-chlorophenyl)ethyl]carbamate (710 mg).

(+)ESI-MS  $m/z$ : 746 (M+Na)<sup>+</sup>

### 25 Preparation 74

Di-tert-butyl dicarbonate (2.18 g) was added to a solution of 2-(4-bromophenyl)ethanamine (2.0 g) in tetrahydrofuran (5 ml) under ice water cooling over 10 minutes and the mixture was stirred at room temperature for  
30 further 1 hour. The reaction mixture was evaporated in vacuo to give tert-butyl 2-(4-bromophenyl)ethylcarbamate (2.98 g) as a colorless foam.

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.43 (9H, s), 2.75 (2H, t, J=8Hz), 3.36 (2H, t, J=8Hz), 7.00-7.10 (2H, m), 7.30-7.50 (2H, m)

35

Preparation 75

The following compound was obtained according to a similar manner to that of Preparation 3.

5

Methyl 4'-[2-[(tert-butoxycarbonyl)amino]ethyl]-1,1'-biphenyl-4-carboxylate

MS m/z: 356 (M+H)

10 Preparation 76

The following compound was obtained according to a similar manner to that of Example 4.

15 Methyl 4'-(2-aminoethyl)-1,1'-biphenyl-4-carboxylate hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 2.80-3.10 (4H, m), 3.88 (3H, s), 7.40 (2H, d, J=8Hz), 7.60-8.10 (6H, m)

Preparation 77

20 To a solution of methyl 4'-(2-aminoethyl)-1,1'-biphenyl-4-carboxylate hydrochloride (420 mg) and benzaldehyde (153 mg) in dichloromethane (5 ml) was stirred for 3 hours, and the mixture was evaporated in vacuo. To the residue in methanol (10 ml) was added sodium borohydride  
25 (65 mg) on ice cooling, and stirred at the same temperature for 1 hour. The resulting mixture was poured into saturated aqueous sodium bicarbonate solution, and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The  
30 residue was chromatographed (hexane - ethyl acetate) over silica gel to afford methyl 4'-[2-(benzylamino)ethyl]-1,1'-biphenyl-4-carboxylate (460 mg) as a colorless powder.

MS m/z: 346 (M+H)

35 Preparation 78

Under nitrogen at 4°C, to a solution of 2,2,2-trifluoro-N-[2-[4-[(4-methoxyphenyl)thio]phenyl]ethyl]-acetamide (1.5 g) in dichloromethane (15 ml) was added 1M boron tribromide in dichloromethane (10.5 ml), and the  
5 mixture was stirred at room temperature for 15 hours. The mixture was evaporated under reduced pressure. The residue was dissolved in a mixture of dichloromethane and saturated aqueous sodium bicarbonate. After separation, the organic layer was dried over magnesium sulfate and evaporated under  
10 reduced pressure to give 2,2,2-trifluoro-N-[2-[4-[(4-hydroxyphenyl)thio]phenyl]ethyl]acetamide (1.42 g).

(+)ESI-MS m/z: 364 (M+Na)<sup>+</sup>

#### Preparation 79

15 To a solution of 2,2,2-trifluoro-N-[2-[4-[(4-hydroxyphenyl)thio]phenyl]ethyl]acetamide (480 mg) in methanol (5.0 ml) was added 1N sodium hydroxide solution (2.8 ml). The mixture was refluxed for 12 hours. The mixture was evaporated under reduced pressure. The residue  
20 was dissolved in a mixture of dichloromethane (40 ml), 1N hydrochloric acid solution (2.0 ml) and water (15 ml). After separation, the organic layer was dried over magnesium sulfate and evaporated under reduced pressure to give 4-[[4-(2-aminoethyl)phenyl]thio]phenol (300 mg).

25 (-)ESI-MS m/z: 244 (M-H)<sup>-</sup>

#### Preparation 80

To a solution of (αS,βR)-4-hydroxynorephedrine (500 mg) and 4-bromophenylethyl bromide (500 mg) in N,N-  
30 dimethylformamide (5 ml) was added N,N-diisopropylethylamine (0.5 ml), and the mixture was stirred for 6 hours at 80°C. The mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residual  
35 oil was diluted in tetrahydrofuran (10 ml). To the solution

was added di-tert-butyl dicarbonate (1 g) at room temperature, and the mixture was stirred at the same temperature for 12 hours. The resulting mixture was evaporated under pressure and the residue was purified by column chromatography on silica gel to give 4-[2-[N-  
5 [(1S,2R)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]-N-(tert-butyloxycarbonyl)amino]ethyl]phenyl bromide (520 mg).

MS m/z: 550 (M+H)

10 Example 57

To a solution of (2R)-N-benzyl-N-[2-(4-bromophenyl)-ethyl]-2-[[tert-butyl(dimethyl)silyl]oxy]-2-(3-chlorophenyl)ethanamine (850 mg) in 1,2-dimethoxyethane (9 ml) was added 4-[[tert-butyl(dimethyl)silyl]oxy]-  
15 phenylboronic acid (498 mg), tetrakis(triphenylphosphine)-palladium (88 mg) and aqueous solution of sodium carbonate (2M, 1.6 ml), and the mixture was stirred at 75°C for 10 hours under nitrogen. The mixture was diluted with ethyl acetate and water. The organic layer was separated, washed  
20 with brine, dried over magnesium sulfate and evaporated. To a solution of the residue in tetrahydrofuran (10 ml) was added 1M tetrabutylammonium fluoride in tetrahydrofuran (3.6 ml), and the mixture was stirred at room temperature for 8 hours under nitrogen. The mixture was partitioned between  
25 ethyl acetate and water. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give 4'-[2-[N-benzyl-N-  
30 [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-1,1'-biphenyl-4-ol (540 mg).

(+)ESI-MS m/z: 458 (M+H)<sup>+</sup>

Example 58

35 A mixture of 4'-[2-[N-benzyl-N-[(2R)-2-(3-

chlorophenyl)-2-hydroxyethyl]amino]ethyl]-1,1'-biphenyl-4-ol (420 mg) in 4N hydrogen chloride in ethyl acetate (1.0 ml) was stirred for 5 minutes. The solvent was removed by evaporation. A suspension of the residue in ethanol (1.5 ml) and chlorobenzene (3.5 ml) was hydrogenated over palladium on carbon (10% w/w, 50% wet, 10 mg) under hydrogen atmosphere for 1 hour. The catalyst was filtered off, and the filtrate was evaporated. The residue was diluted with chloroform (40 ml) and methanol (5 ml). The organic layer was washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure. To the residue was added tetrahydrofuran (3 ml) and di-tert-butyl dicarbonate (220 mg), and the mixture was stirred at room temperature for 12 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give tert-butyl (2R)-N-[2-(3-chlorophenyl)-2-hydroxyethyl]-N-[2-(4'-hydroxy-1,1'-biphenyl-4-yl)ethyl]carbamate (245 mg).

(+)ESI-MS m/z: 490 (M+Na)<sup>+</sup>

#### Example 59

To a solution of tert-butyl (2R)-N-[2-(3-chlorophenyl)-2-hydroxyethyl]-N-[2-(4'-hydroxy-1,1'-biphenyl-4-yl)ethyl]carbamate (240 mg) and potassium carbonate (78 mg) in N,N-dimethylformamide (4 ml) was added tert-butyl bromoacetate (110 mg), and the mixture was stirred at room temperature for 3 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 3/1) to give tert-butyl [[4'-[2-[N-

(tert-butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-1,1'-biphenyl-4-yl]oxy]acetate (245 mg).

(+)ESI-MS  $m/z$ : 582 (M+H)<sup>+</sup>

5

#### Example 60

The following compounds were obtained according to a similar manner to that of Example 4.

- 10 (1) [[4'-[2-[[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]ethyl]-1,1'-biphenyl-4-yl]oxy]acetic acid hydrochloride
- NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 3.02-3.35 (6H, m), 4.72 (2H, s),  
5.00-5.05 (1H, m), 6.37 (1H, br), 6.99 (2H, d,  
15 J=8.7Hz), 7.30-7.61 (10H, m), 9.04 (1H, br), 13.03  
(1H, br)
- (-)ESI-MS  $m/z$ : 424 (M-HCl-H)<sup>-</sup>

- 20 (2) [4-[4-[2-[[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]ethyl]benzoyl]phenoxy]acetic acid hydrochloride
- NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 3.01-3.32 (6H, m), 4.81 (2H, s),  
4.96-5.00 (1H, m), 6.35 (1H, br), 7.07 (2H, d,  
J=8.8Hz), 7.35-7.47 (6H, m), 7.66-7.75 (4H, m),  
8.99 (1H, br)
- 25 (-)ESI-MS  $m/z$ : 452 (M-HCl-H)<sup>-</sup>

#### Example 61

- To a solution of tert-butyl N-[2-(4-bromophenyl)ethyl]-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate (435 mg)
- 30 in 1,2-dimethoxyethane (6 ml) were added 4-methoxycarbonyl-phenyl boronic acid (224 mg), tetrakis(triphenylphosphine)-palladium (55 mg) and aqueous solution of sodium carbonate (2M, 1.0 ml), and the mixture was stirred at 80°C for 2 hours under nitrogen. The mixture was diluted with ethyl
- 35 acetate and water. The organic layer was separated, washed

with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 3/1) to give methyl 4'-[2-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-1,1'-biphenyl-4-carboxylate (400 mg).

(+)ESI-MS m/z: 510 (M+H)<sup>+</sup>

#### Example 62

The following compound was obtained according to a similar manner to that of Example 6.

4'-[2-[[ (2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-ethyl]-1,1'-biphenyl-4-carboxylic acid hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 3.01-3.27 (6H, m), 5.01-5.06 (1H, m), 6.36 (1H, br), 7.34-7.48 (6H, m), 7.70-7.81 (6H, m), 8.02 (2H, d, J=8.4Hz), 9.11 (1H, br)

(-)ESI-MS m/z: 394 (M-HCl-H)<sup>-</sup>

#### Example 63

To a solution of [4-[2-[N-benzyl-N-[(2R)-2-[[tert-butyl(dimethyl)silyl]oxy]-2-(3-chlorophenyl)ethyl]amino]-ethyl]phenyl][4-[[tert-butyl(dimethyl)silyl]oxy]phenyl]-methanol (1.1 g) in tetrahydrofuran (15 ml) was added 1M tetrabutylammonium fluoride in tetrahydrofuran (5.0 ml) at 0°C, and the mixture was stirred at room temperature for 24 hours under nitrogen. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give 4-[[4-[2-[N-benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-phenyl](hydroxy)methyl]phenol (550 mg).

(+)ESI-MS m/z: 486 (M-H)<sup>-</sup>

Example 64

A mixture of 4-[[4-[2-[N-benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl](hydroxy)-methyl]phenol (545 mg) in 4N hydrogen chloride in 1,4-dioxane (1.0 ml) was stirred for 5 minutes. The solvent was removed by evaporation. A suspension of the residue in ethanol (2.2 ml) and chlorobenzene (5.2 ml) was hydrogenated over palladium on carbon (10% w/w, 50% wet, 55 mg) under hydrogen atmosphere for 2 hours. The catalyst was filtered off, and the filtrate was evaporated. The residue was diluted with ethyl acetate and saturated sodium bicarbonate solution. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give 4-[4-[2-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]benzyl]phenol (395 mg).

(+)ESI-MS m/z: 382 (M+H)<sup>+</sup>

Example 65

To a solution of 4-[4-[2-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]benzyl]phenol (390 mg) in tetrahydrofuran (3.5 ml) and water (3.5 ml) was added di-tert-butyl dicarbonate (223 mg), and the mixture was stirred at room temperature for 30 minutes. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give tert-butyl (2R)-N-[2-(3-chlorophenyl)-2-hydroxyethyl]-N-[2-[4-(4-hydroxybenzyl)phenyl]ethyl]carbamate (480 mg).

(+)ESI-MS m/z: 482 (M+H)<sup>+</sup>

Example 66

The following compounds were obtained according to a similar manner to that of Example 57.



(1) tert-Butyl [4-[4-[2-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]benzyl]-phenoxy]acetate

(+)ESI-MS m/z: 598 (M+H)<sup>+</sup>

5

(2) tert-Butyl [4-[4-[2-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]benzoyl]-phenoxy]acetate

(+)ESI-MS m/z: 610 (M+H)<sup>+</sup>

10

#### Example 67

A solution of tert-butyl [4-[4-[2-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino]ethyl]benzyl]phenoxy]acetate (240 mg) and 4N

15 hydrochloride in 1,4-dioxane (3.0 ml) was stirred at room temperature for 24 hours. The mixture was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (methanol/acetic

20 acid/chloroform = 10/1/100) to give a product. To a tetrahydrofuran (2.0 ml) solution of the product, 4N hydrogen chloride in 1,4-dioxane (1.0 ml) was added. The mixture was stirred for 5 minutes and evaporated under reduced pressure to give [4-[4-[2-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]benzyl]phenoxy]acetic acid

25 hydrochloride (72 mg).

NMR (DMSO-d<sub>6</sub>, δ): 2.91-3.24 (6H, m), 3.84 (2H, s), 4.61 (2H, s), 4.94-4.99 (1H, m), 6.32 (1H, br), 6.80 (2H, d, J=8.7Hz), 7.10-7.21 (6H, m), 7.29-7.46 (4H, m), 8.89 (1H, br)

30 (-)ESI-MS m/z: 438 (M-HCl-H)<sup>-</sup>

#### Example 68

The following compound was obtained according to a similar manner to that of Example 61.

35

tert-Butyl N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-  
N-[2-[4-(4-hydroxybenzoyl)phenyl]ethyl]carbamate  
(+)ESI-MS m/z: 496 (M+H)<sup>+</sup>

5 Example 69

A solution of methyl 4'-[2-(benzylamino)ethyl]-1,1'-  
biphenyl-4-carboxylate (460 mg), and 2-chloro-5-[(2R)-2-  
oxiranyl]pyridine (207 mg) in ethanol (10 ml) was refluxed  
for 18 hours. The mixture was evaporated in vacuo. The  
10 residue was purified by column chromatography on silica gel  
(chloroform:methanol = 100:1) to give methyl 4'-[2-[N-benzyl-  
N-[(2R)-2-(6-chloro-3-pyridyl)-2-hydroxyethyl]amino]ethyl]-  
1,1'-biphenyl-4-carboxylate (470 mg) as a colorless foam.  
MS m/z: 501 (M+H)

15

Example 70

Methyl 4'-[2-[N-benzyl-N-[(2R)-2-(6-chloro-3-pyridyl)-  
2-hydroxyethyl]amino]ethyl]-1,1'-biphenyl-4-carboxylate (470  
mg), ammonium formate (296 mg) and palladium on carbon  
20 powder (100 mg) in methanol (10 ml) and water (1.0 ml) was  
refluxed for 30 minutes. The reaction mixture was filtrated  
and poured into water and extracted with ethyl acetate. The  
organic layer was washed with brine, dried over magnesium  
sulfate, and evaporated in vacuo. A mixture of the residue  
25 was chromatographed (chloroform-methanol) over silica gel to  
give methyl 4'-[2-[[2-(2-hydroxy-2-(3-pyridyl)ethyl]-  
amino]ethyl]-1,1'-biphenyl-4-carboxylate (326 mg) as a  
colorless foam.

MS m/z: 377 (M+H)

30

Example 71

At room temperature, to a solution of methyl 4'-[2-  
[[2-(2-hydroxy-2-(3-pyridyl)ethyl]amino]ethyl]-1,1'-  
biphenyl-4-carboxylate (326 mg) in methanol was added 1N  
35 sodium hydride (0.87 ml), and the mixture was stirred at the

same temperature for 3 hours. The resulting mixture was evaporated under reduced pressure and dried to give sodium 4-[4-[2-[[ (2R)-2-hydroxy-2-(3-pyridyl)ethyl]amino]ethyl]]-1,1'-biphenyl-4-carboxylate (220 mg) as a colorless powder.

NMR (DMSO- $d_6$ ,  $\delta$ ): 2.50-2.80 (6H, m), 4.70 (1H, t,  $J=6\text{Hz}$ ), 7.10-7.40 (3H, m), 7.50-7.70 (5H, m), 7.90-8.00 (1H, m), 8.40-8.50 (2H, m)

MS  $m/z$ : 361 (M-H)

#### Example 72

4-[[4-(2-Aminoethyl)phenyl]thio]phenol (295 mg) and (2R)-2-(3-chlorophenyl)oxirane (186 mg) in ethanol (3.5 ml) was refluxed for 6 hours. The mixture was evaporated. The residue was purified by column chromatography on silica gel (chloroform/methanol = 100/3) to give 4-[[4-[2-[[ (2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]thio]phenol (155 mg).

(+)ESI-MS  $m/z$ : 400 (M+H)<sup>+</sup>

#### Example 73

To a solution of tert-butyl N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-N-[2-[4-[(4-hydroxyphenyl)thio]phenyl]ethyl]carbamate (195 mg) and potassium carbonate (59 mg) in N,N-dimethylformamide (3 ml) was added tert-butyl bromoacetate (84 mg), and the mixture was stirred at room temperature for 3 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 3/1) to give tert-butyl [4-[[4-[2-[N-(tert-butoxycarbonyl)-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]thio]phenoxy]acetate (168 mg).

120

(+)ESI-MS m/z: 636 (M+Na)

5

10

15

20

25

30

35